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THE EARLY AND REMOTE EFFECTS OF TOTAL AND PARTIAL PARAVERTEBRAL SYMPATHECTOMY ON BLOOD PRESSURE*

AN EXPERIMENTAL STUDY

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THERE has been a renewed interest in the effects of sympathetic ganglionectomy and sympathetic neurotomy in recent years as a result of the employment of these procedures in the treatment of vascular disturbances in the limbs and of essential hypertension. Cannon, Newton, Bright, Menkin, and Moore,[1] in their studies of the general effects of complete paravertebral sympathectomy in cats, observed lowering of blood pressure in the one case where it was mentioned. Bradley Cannon[2] noted a fall at the completion of sympathectomy but did not determine how long it lasted. Wilson, Roome and Grimson[3] made frequent readings by arterial punctures for two to seven weeks following complete sympathectomy on 13 dogs and observed falls averaging 37 Mm. of mercury after one week with slight rises in subsequent weeks. But in the longest experiment the pressure did not approach the preoperative level. No published studies were found of the early and remote effects on blood pressure in normal dogs of partial ganglionectomy and splanchnectomy as introduced by Peet[4] and of partial thoracolumbar anterior root section as introduced by Adson[5] and Page and Heuer[6] for the relief of essential hypertension in man.

In this experimental study on dogs, an attempt has been made to obtain additional evidence concerning both early and late effects of complete and partial removal of the paravertebral sympathetic chains and of partial anterior spinal rhizotomy on the blood pressure and circulation.

EFFECTS OF COMPLETE SYMPATHECTOMY.—In the procedure of complete paravertebral sympathectomy performed under ether anesthesia, an attempt was made to remove the sympathetic chains on both sides from above the stellate ganglion to the hollow of the sacrum, usually the second or third sacral ganglion, in three stages at ten to 30 day intervals, first one side of the chest, then the other, and finally the abdomen. Leaving the small terminal, sacrococcygeal chain because of difficulty of removal has been found to have no influence on general reactions.

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Anatomy.—The cervical sympathetic chain in the dog is fused with the vagus. The stellate ganglion is connected to the vagus by one or two large nerves. It is also connected by a short thick nerve to the first thoracic nerve and by other smaller nerves to the second and third intercostal nerves, the brachial plexus, the plexus about the heart and lungs, and the thoracic sympathetic chain. The thirteen intercostal nerves on each side all have connections with the sympathetic chain. In most instances these are single nerves varying from 3 Mm. in length in the midthoracic region to 12 to 15 Mm. in length near the stellate and near the diaphragm, and represent fused gray and white rami. In the midthoracic region, however, the segmental connections between the sympathetic chain and intercostal nerves are occasionally double and presumably represent separate gray and white rami. In the abdomen single connections exist between the lumbar segmental nerves and the lumbar and sacral plexus and the sympathetic chain. The greater splanchnic nerve originates in the lower thoracic chain and passes through the diaphragm as a large nerve. The lesser splanchnics are variable and originate near the diaphragmatic crura. At operation all connections of the sympathetic chain were severed within a few millimeters of the ganglia, except the greater splanchnic and the connection between the stellate and the vagus. These were severed 5 to 15 Mm. from the ganglia. It was considered that no general effects would arise from failure to remove the small amount of sacrococcygeal chain left because of technical difficulty of removal.

Direct blood pressure readings were made on all dogs with a mercury manometer before (an average of three interval readings), during and after the sympathectomy by puncture of the femoral artery. When operated upon in the above mentioned order, there was usually a slight fall after the first chest operation, whether right or left, which was recovered from promptly, but with the second chest operation the pressure fell, usually 35 to 75 Mm. of mercury. This was followed by some rise but the pressure usually remained lowered by 25 to 50 Mm. of mercury. Removal of the abdominal chains caused little or no further fall in blood pressure.

Early and remote effects on blood pressure, blood volume, blood viscosity, cardiac output and pulse rate were studied.

Early Effects.—In determining the early effects, nine dogs were observed for periods varying from three to 42 days following completion of the sympathectomy before they were sacrificed in a variety of experiments. The blood pressure which averaged 155 Mm. of mercury before operation remained lowered constantly, the average reduction being 38 Mm. of mercury. Blood volume determinations were made on four dogs, once before and once shortly after sympathectomy, and the results were practically identical. There was no decrease to explain the lowered blood pressure nor was there any increase such as might be expected in the event of an appreciable dilatation of the vascular bed (Table I). Blood viscosity measured, once before and once immediately after sympathectomy, in four dogs showed no change (Table II). The minute cardiac output estimated twice before and twice soon after opera-

tion in four dogs averaged 28 per cent lower in the postoperative series than in the preoperative series (Table III). The pulse rate in three dogs slowed as a result of the operation averaging per minute 109 before and 69 after.

TABLE I

BLOOD VOLUME BEFORE AND AFTER COMPLETE SYMPATHECTOMY
(Congo Red Plasma Dye Method)

Dog	Date	Weight	Preop. Bl. Vol.	Interval of Three Stage Sympathectomy	Date	Weight	Postop. Bl. Vol.
No. 187	11/ 4/35	11.0 Kg.	906 cc.	11/21/35 to 1/29/35	3/5/36	11.27 Kg.	1,143 cc.
No. 379	10/24/35	16.3 Kg.	1,996 cc.	11/12/35 to 1/29/35	3/5/36	18.75 Kg.	1,761 cc.
No. 380	10/24/35	13.25 Kg.	1,581 cc.	10/28/35 to 1/ 3/35	2/3/36	12.35 Kg.	1,686 cc.
No. 383	10/24/35	13.82 Kg.	1,641 cc.	10/25/35 to 12/20/35	2/3/36	13.7 Kg.	1,570 cc.
Average.....		13.59 Kg.	1,531 cc.	Average.....		14.02 Kg.	1,540 cc.

TABLE II

BLOOD VISCOSITY (OSWALD VISCOSIMETER) BEFORE AND AFTER COMPLETE SYMPATHECTOMY

Dog	Date	Blood Viscosity	Interval of Three-Stage Sympathectomy	Date	Blood Viscosity
No. 143	2/ 7/36	7.16	2/26/36 to 4/23/36	5/17/36	8.28
No. 309	2/ 7/36	4.40	2/17/36 to 4/ 9/36	5/17/36	5.07
No. 310	2/ 7/36	6.81	2/17/36 to 4/23/36	5/17/36	6.69
No. 537	3/19/36	7.60	5/ 4/36 to 6/24/36	7/ 3/36	7.58
Average.....		6.49		Average.....	6.90

TABLE III

CARDIAC OUTPUT (FICK FORMULA, USING DIRECT RIGHT HEART AND FEMORAL ARTERY PUNCTURES)

Dog	Date	Weight	C. O.	Interval of Three-Stage Sympathectomy	Date	Weight	C. O.
No. 751	10/ 2/36	9.75 Kg.	1,815 cc./min.	10/14/36 to	11/25/36	8.15 Kg.	1,518 cc./min.
	10/ 2/36	9.55 Kg.	2,565 cc./min.	11/20/36	11/25/36	8.15 Kg.	1,489 cc./min.
No. 143	1/22/36	9.25 Kg.	3,177 cc./min.	2/26/36 to	5/27/36	8.78 Kg.	2,081 cc./min.
	1/22/36	9.25 Kg.	3,523 cc./min.	4/23/36	5/29/36	8.75 Kg.	2,560 cc./min.
No. 522	4/30/36	15.5 Kg.	4,752 cc./min.	5/ 5/36 to	8/ 6/36	14.75 Kg.	3,155 cc./min.
	5/ 4/36	14.8 Kg.	4,406 cc./min.	6/24/36	8/ 6/36	14.75 Kg.	3,508 cc./min.
No. 537	3/23/36	12.5 Kg.	5,821 cc./min.	5/ 4/36 to	8/13/36	11.0 Kg.	3,784 cc./min.
	4/13/36	12.15 Kg.	3,377 cc./min.	6/24/35	8/13/36	10.7 Kg.	3,000 cc./min.
Average.....		11.59 Kg.	3,679 cc./min.	Average.....		10.63 Kg.	2,637 cc./min.

The fact that despite the lowered cardiac output and slight bradycardia a blood pressure averaging 117 Mm. of mercury was maintained shows that the animals suffered only moderate lowering of peripheral resistance as a result of the sympathectomy. This indicates that there is an inherent vascular tone which assists in the maintenance of the blood pressure at a reduced level immediately after sympathectomy.

Late Effects.—The late effects were observed in 14 dogs over periods varying from six to 23 months, averaging 13 months. The blood pressure readings were made about weekly for a month, about every three weeks for the following five months, and after that at irregular intervals up to two

months in the longest experiments. The average mean systolic pressure preoperatively was 147 Mm. of mercury and that during the first month after sympathectomy was 110 Mm. of mercury, giving an average fall of 37 Mm. of mercury. In ten dogs the pressure gradually increased from the early postoperative levels to reach the preoperative levels in two to nine months, the average being five and three-quarter months. Chart 1 shows the blood pressure readings in one case and demonstrates the late restoration of blood pressure. In three dogs the preoperative level had not been reached at the time they were sacrificed. One of these recovered 50 per cent of the loss in seven and one-half months, at which time death occurred from a sudden but undetermined cause. Another dog had a gradual rise in pressure for 12 months until 75 per cent of the loss had been regained, when death occurred from acute urinary

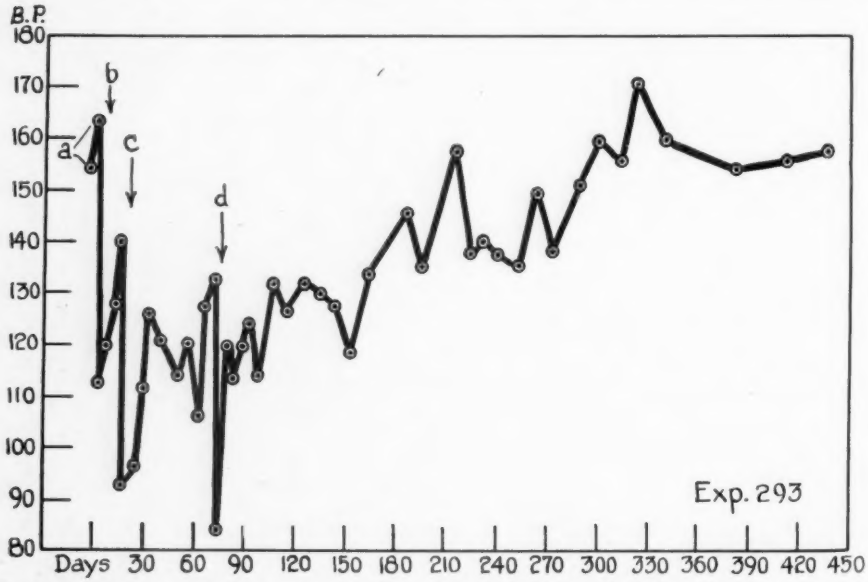

CHART 1.—Graph of mean blood pressure of dog. (*a*) Preoperative. (*b*) After right chest sympathectomy. (*c*) After left chest sympathectomy. (*d*) After abdominal sympathectomy.

tract infection. The third dog gradually recovered 75 per cent of the loss in nine months, after which the pressure remained about constant until the animal was sacrificed 18 months postoperatively. In one young dog the preoperative pressure was equaled in two months and exceeded by 20 Mm. in six months, when death from intercurrent infection took place.

Blood volume determinations were made on four dogs which had recovered their preoperative pressure levels. They averaged 107 cc. per Kg. as compared with 111.5 cc. per Kg. in 30 determinations on normal dogs. In four recovered dogs the blood viscosity was found to be within normal limits. The pulse rate of ten recovered dogs averaged 92 per minute as compared with 113 per minute in nine normal dogs. The minute cardiac output in five recovered dogs averaging 13.25 Kg. in weight showed an average of 2.198 cc. per minute. Twenty-four normal dogs averaging 10.1 Kg. in weight had an average cardiac output of 2,862 cc. per minute.

With no change in blood volume or viscosity and with a continued lowering of minute cardiac output, the gradual slow rise of blood pressure with a return to preoperative levels in the great majority of cases is indicative of concomitant increase in vascular tone.

After complete sympathectomy, both early and late, the behavior of the dogs under laboratory conditions was practically normal. No tests were made of their ability to do work but Brouha, Cannon, and Dill[7] have shown that completely sympathectomized dogs have a decrease in ability to do work on a treadmill early with complete recovery in about three months.

Mechanism of Recovery of Blood Pressure.—An important point to be determined is the mechanism by which the blood pressure is restored to normal in the recovered dogs. This might be a central mechanism as regenerated cardiovascular or adrenal sympathetics or extrasympathetic nerve fibers of the somatic system, either subserving vasoconstrictors which become activated or vasodilators which become inhibited. It might also be in part or whole a peripheral mechanism as independent activity of local nerve ganglia along the blood vessels or chemical action on the blood vessels, especially the finer arterioles and capillaries.

The possible rôle of a restituted central mechanism was studied functionally in both the recently sympathectomized and recovered dogs by section and stimulation of the spinal cord at the eighth cervical segment, by somatic nerve stimulation, by stimulation of vasomotor centers in the hypothalamus, and by elevation of intracranial pressure.

Section and Stimulation of Spinal Cord and Sciatic Nerve.—In five recently sympathectomized dogs, the spinal cord at the eighth cervical segment and a sciatic nerve were exposed under barbital anesthesia. Blood pressure was recorded from a carotid cannula. Sciatic stimulation with make and break and tetanizing currents of different strengths gave inconstant results. Slight to moderate falls were obtained in all cases but the strength and type of current producing them was variable for each case. No rises were obtained. The spinal cord was then sectioned. This resulted in very slight temporary fall of blood pressure in two cases and no change in three. Faradic stimulation of the cut distal end caused slight to moderate falls in four of the five cases. Restimulation of the sciatic nerve after cord section in three cases caused no change in blood pressure. Chart 2 shows the effect of cord section and of stimulation of the distal segment of the cut cord in a dog four days after completing the sympathectomy, which lowered the blood pressure from about 152 to 94 Mm. of mercury. The rises in blood pressure seen in normal dogs when vasoconstrictor fibers are stimulated by cutting the cord and by the application of a tetanizing current to the distal cut end were absent. Instead, in four of five experiments, temporary lowering of the blood pressure in response to cord stimulation was observed. Also the gradual fall in blood pressure seen in normal dogs after the cord section has eliminated central vasomotor tone was not observed in any of these five recently sympathectomized dogs.

In three sympathectomized dogs observed for 567, 516 and 549 days respectively, whose blood pressures had returned to preoperative levels, sciatic nerve stimulation caused essentially no change in blood pressure in two and moderate falls with weak make and break and tetanizing currents in one. Cord section caused a slight rise followed by a gradual fall, and distal cord stimulation caused a marked and rapid rise in blood pressure. Chart 3 shows the effect of cord section and stimulation of the distal segment in a dog 516

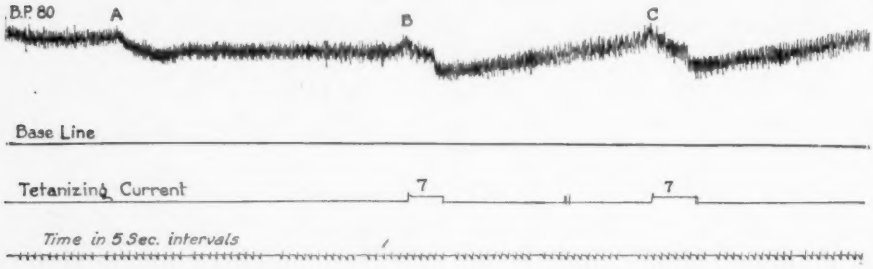

CHART 2.—Blood pressure tracing of recently sympathectomized dog. (*a*) After 8th cervical cord section. (*b*) and (*c*) After stimulation of cut end of distal segment of cord.

days after sympathectomy, and 390 days after restoration of blood pressure to the preoperative level. As the cord was cut, and again as the distal cut end was stimulated, abrupt increases in blood pressure were observed. Also 20 seconds after division of the cord, a decline in blood pressure began. These findings resemble those observed in normal dogs where stimulation of vasoconstrictor fibers of the cord gives blood pressure elevation, and cord section removes central vasopressor tone and causes a blood pressure decline.

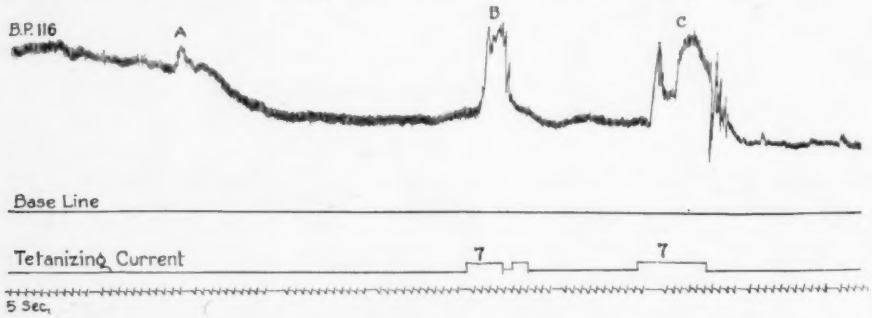

CHART 3.—Blood pressure tracing of dog 516 days after complete sympathectomy and 390 days after restoration to preoperative level. At A, spinal cord sectioned. At B and C, cut end of distal segment stimulated.

Hypothalamic Stimulation (performed by Dr. F. Keith Bradford, Service of Neurosurgery).—The hypothalamus was stimulated in four normal dogs, in two dogs sympathectomized 28 and 39 days previously with their blood pressures lowered, and in two other dogs sympathectomized 391 and 690 days previously with blood pressure restored to the preoperative levels. A modification of the Horsley-Clarke[8] steriotaximeter as used by Ranson[9] in cats was adapted for use in dogs by moving the slides supporting the ear plugs 30 Mm. posteriorly and modifying the vise to grip the dogs between the

orbit and the upper teeth. The coördinates required to place a bipolar electrode into various regions of the hypothalamus were roughly determined by postmortem studies on dogs. The animals used in the experiment were anesthetized with ether. After exposing and reflecting the dura over the convexity of the brain, the electrode was run down through the brain into the hypothalamus two to 14 times, and 12 to 30 areas were stimulated with each descent of the electrode. The areas stimulated were determined by study of serial sections of the brain.

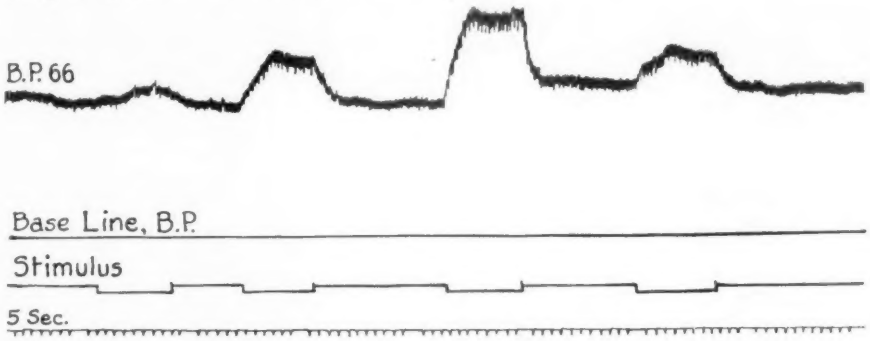

CHART 4.—*Normal Dog:* Elevation of blood pressure from faradic stimulation of hypothalamus in the region of the anterolateral wall of 3rd ventricle.

In four normal dogs stimulation of the hypothalamus in the regions about the supra-optic nuclei, about the walls of the anterior portion of the third ventricle, and posteriorly above the pituitary body gave abrupt elevations of blood pressure. Chart 4 shows the response in one animal. The average increases were respectively 20, 33, 23, and 15 Mm. of mercury when a tetanizing stimulus of six or seven on a Harvard inductorium was used. In two of these dogs stimulation of neighboring areas of the hypothalamus gave blood pressure lowering.

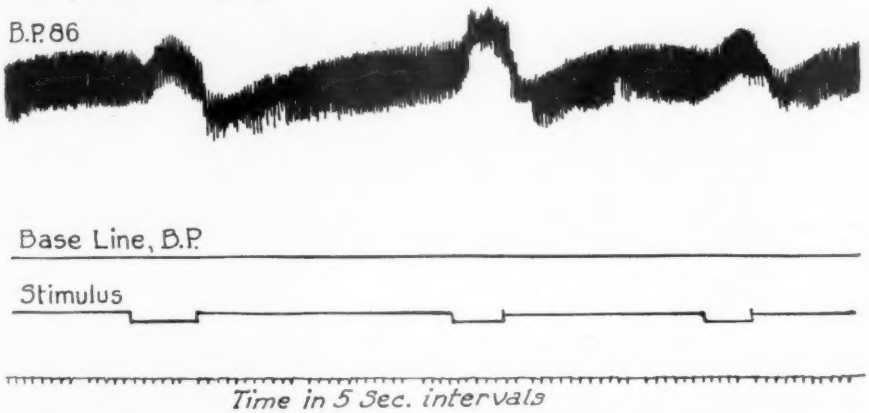

CHART 5.—Completely sympathectomized dog 391 days after operation and five months after return of blood pressure to preoperative level. Elevation of blood pressure from faradic stimulation of hypothalamus in region of anterolateral wall of 3rd ventricle.

A systematic exploration of the hypothalamus of the two recently sympathectomized dogs, using the same technic, failed to elicit any blood pressure

elevation. Blood pressure lowering was obtained in one dog. Serial sections of the brains showed that the exploring electrode had made nine descents in one dog and 12 in the other through regions of the hypothalamus that in normal dogs had given blood pressure elevations.

Similar exploration in the two dogs with restored blood pressure elicited elevations averaging 11 Mm. of mercury in the one and 12 Mm. of mercury in the other. Chart 5 shows the response in one animal. Serial sections of the brain revealed that the stimulation giving these pressor responses had been made as in the normal dogs in the hypothalamic regions about the supra-optic nuclei, about the walls of the anterior portion of the third ventricle, and occasionally posteriorly above the pituitary body.

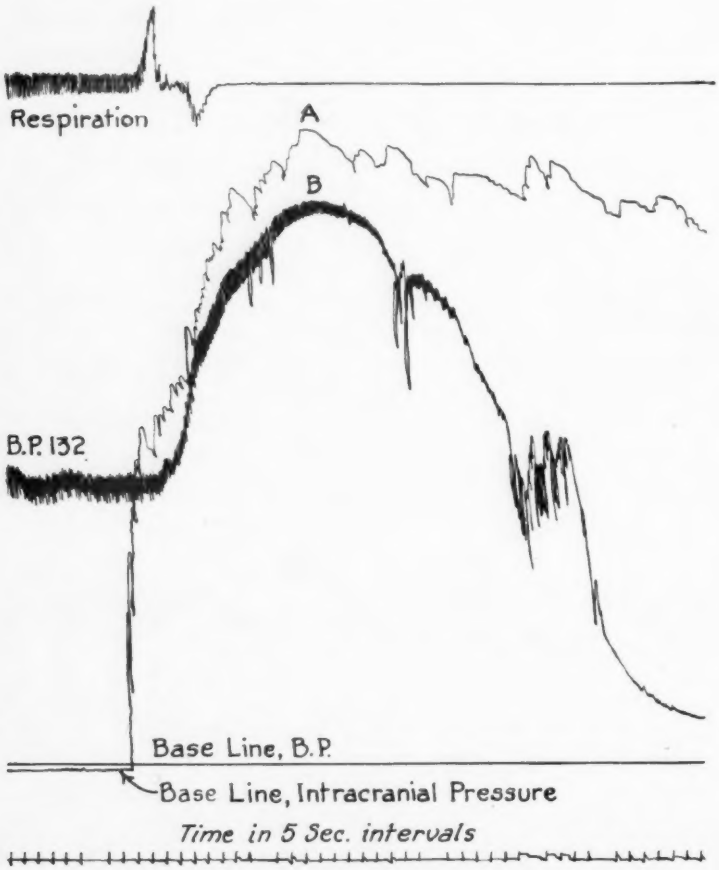

CHART 6.—Effect of increased intracranial pressure on blood pressure of normal dog.

Effect of Elevation of Intracranial Pressure.—Rapid and marked elevation of intracranial pressure in normal dogs by the forceful introduction of saline through a water tight trocar bored through the skull causes a marked rise in blood pressure with failure of respiration and then cardiac failure and death

in three to four minutes. This intracranial pressure among other things stimulates the vasopressor centers of the brain stem. Chart 6 shows response of a normal dog under barbital anesthesia to increased intrcranial pressure. Ten normal dogs were tested. The average increase above the control blood pressure was 146 Mm. of mercury, and the range was between 102 and 202 Mm. of mercury.

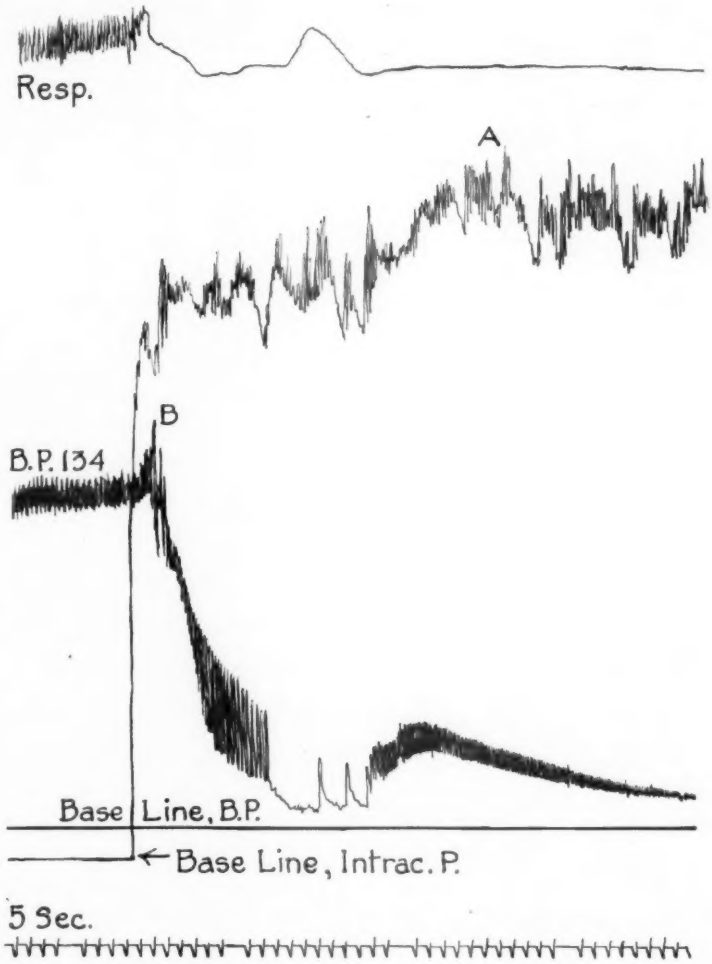

CHART 7.—Effect of increased intracranial pressure in recently sympathectomized dog.

The experiment was performed on two recently sympathectomized animals. The first, 12 days after operation, had a systolic blood pressure around 142 Mm. as compared with a preoperative blood pressure of 162 Mm. of mercury. The respirations ceased and the blood pressure declined rapidly with death in three and one-half minutes (Chart 7). In this dog the vagi were intact and a marked vagal-cardiac inhibition was observed. In another dog, 26 days after sympathectomy, with a blood pressure of 120 Mm. as com-

pared with a preoperative level of 174 Mm., the vagi were first divided and the decline in blood pressure with increased intracranial pressure was more gradual; but respiration ceased promptly, no increase of blood pressure developed, and death occurred in about the same length of time. Neither of these recently sympathectomized dogs showed any blood pressure increase that would suggest the stimulation of vasoconstrictor centers such as occurs in normal dogs.

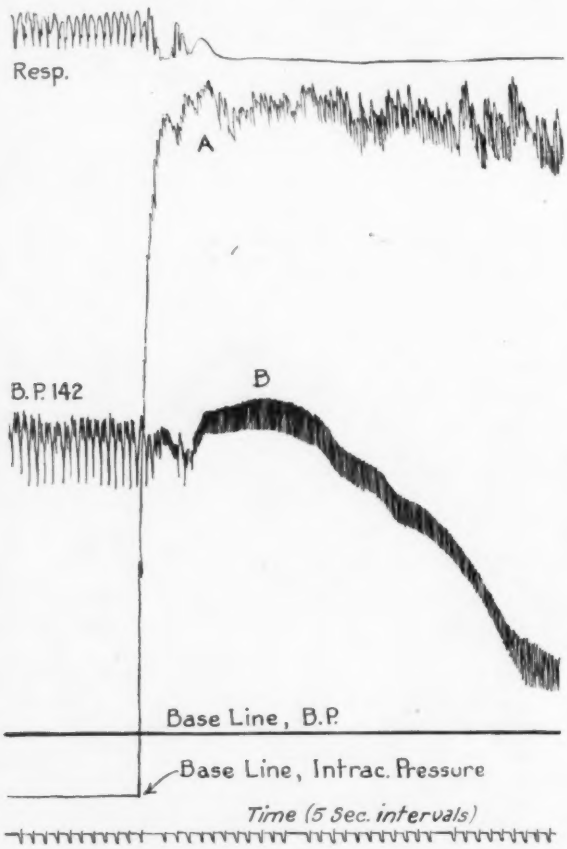

CHART 8.—Effect of increased intracranial pressure on dog 23 months after sympathectomy and 17 months after return of blood pressure to preoperative level.

This same experiment was performed on one dog 696 days after operation when the blood pressure had been back to the preoperative level for 17 months. The vagi were left intact (Chart 8). There was an increase of blood pressure of 12 Mm. of mercury, which was maintained for about 60 seconds, after which a rapid decline occurred. Respirations ceased at the beginning and death occurred within four minutes. This dog met the emergency of increased intracranial pressure slightly better than the recently sympathectomized dogs, but fell far short of the vasopressor responses of the normal animal.

DISCUSSION.—The loss of the vasopressor response in recently sympathectomized dogs, upon whom cord section and distal cord stimulation, hypothalamic stimulation, sciatic stimulation and elevation of intracranial pressure were carried out, demonstrates that the sympathectomy completely eliminates the existing central nervous vasopressor control. It is noteworthy, however, that vasodepressor responses were still obtainable. The vasopressor response on stimulation of hypothalamus and spinal cord of sympathectomized dogs whose blood pressures had been restored to preoperative levels is indicative of the reëstablishment of some degree of central vasopressor control. The gradual decline in blood pressure that followed cord section in three dogs 567, 516, and 549 days after sympathectomy suggests that some degree of vasomotor tone is also present. However, the pressor responses to tetanizing sciatic stimulation and in one case to increased intracranial pressure were very slight.

Regeneration of Sympathetic Nerves.—Attempts have been made to determine the nature of this restituted mechanism of central vasopressor control, but the results have been rather meager and inconclusive. Regeneration of the excised nerves was considered and necropsy dissections of the fields of operation were carried out on both recently operated and recovered animals.

Langley,[10] Tsukaguchi,[11] Lee,[12] Tower and Richter[13] and others have published results of experiments showing that section of preganglionic fibers in various regions is usually followed by regeneration and restoration of function, in three to eight weeks. Smithwick[14] and others observed restoration of function after severing preganglionic fibers of the thoracic chain between the second and third thoracic ganglia in man.

Tuckett,[15] and Kilvington and Osborne[16] have obtained evidence of regeneration in case of experimental division of postganglionic fibers in various regions.

There is no reliable experimental evidence that divided pre- and postganglionic fibers become connected with functional restoration where the synaptic ganglion of the postganglionic fiber has been excised. Tower and Richter[17] failed to find evidence of such regeneration one and one-half years after ganglion excision.

Dissection of the nine recently sympathectomized animals showed that the sympathetic chains had been completely removed in eight and that in one a portion of the left stellate ganglion and its connection with the first thoracic nerve had been left behind. The blood pressure of this animal averaged 26 Mm. of mercury lower than before operation and in the terminal experiment of increased intracranial pressure there was no vasopressor response. In all experiments a single stump on each spinal nerve represented what was left of fused gray and white rami. The stumps had grown little or none and varied from 2 to 12 Mm. in length, being shortest in the midthoracic region. Microscopic examination of four of these stumps showed no turning back of fibers which could represent a growth of the white ramus into the cut end of gray ramus.

Dissection was made of the 14 dogs sacrificed seven and one-half to 23 months postoperatively, with return of pressures to preoperative levels in 11 and extensive but incomplete return in the other three. In one case an overlooked portion of chain was found in the region of the left eleventh, twelfth and thirteenth intercostals, with fibers converging into a splanchnic nerve which ran to the left adrenal. The animal was sacrificed by an intracranial pressure elevation experiment and the blood pressure after an initial lag rose about one-half as high as in a normal animal. This was interpreted as indicating the

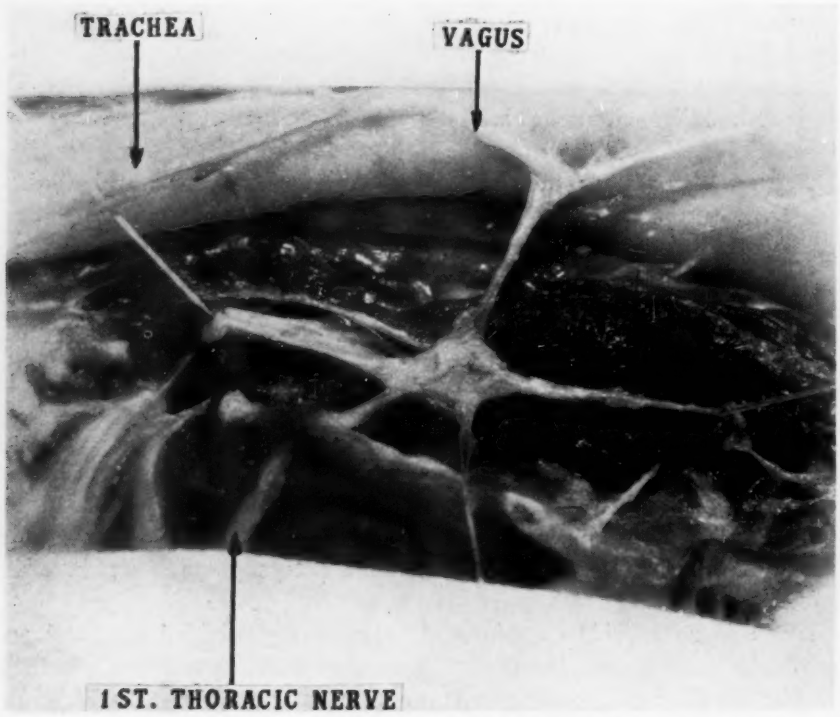

FIG. 1.—Dissection showing scar and strands at site of right stellate excision 11 months previously.

presence of adrenal function. In another a ganglion was found just beneath the diaphragm which was connected with the spinal nerve and sent two small fibers to the left adrenal. These were the only apparently overlooked portions of the sympathetic chain in the 14 animals.

The stumps of the old divided sympathetic rami on the anterior divisions of the spinal nerves were dissected. In the majority of instances from the first thoracic to the second or third lumbar, they were found to be 1 to 3 cm. long, and their ends were fused with the overlying scar tissue. Strands of tissue ran irregularly along the course of the pleural scar at the sites of excision of the chains, but dissection of the stumps from the scar usually failed to establish any lengthy continuity between them and the strands. Below the second or third lumbar, where the lowermost white rami emerge, no outgrown stumps were found. Occasionally an intercostal stump ended

in a bulb analogous to the amputation neuroma frequently seen on a cut somatic nerve.

In all cases there were strands connected with a scar in the region of removal of the stellate ganglion. Some of them ran from the first, second and even third intercostal stumps; and most constantly there were one or two extending to the divided stump that previously connected the stellate and vagus. Occasionally fine strands ran from the scar to the roots of the brachial plexus. In most instances the strands looked grossly like scar tissue, but they offered the possibility of preganglionic sympathetic pathways to the brachial plexus and the vagus. Fig. 1 shows a dissection of the right cervicothoracic region 11 months after complete sympathectomy, with return of the

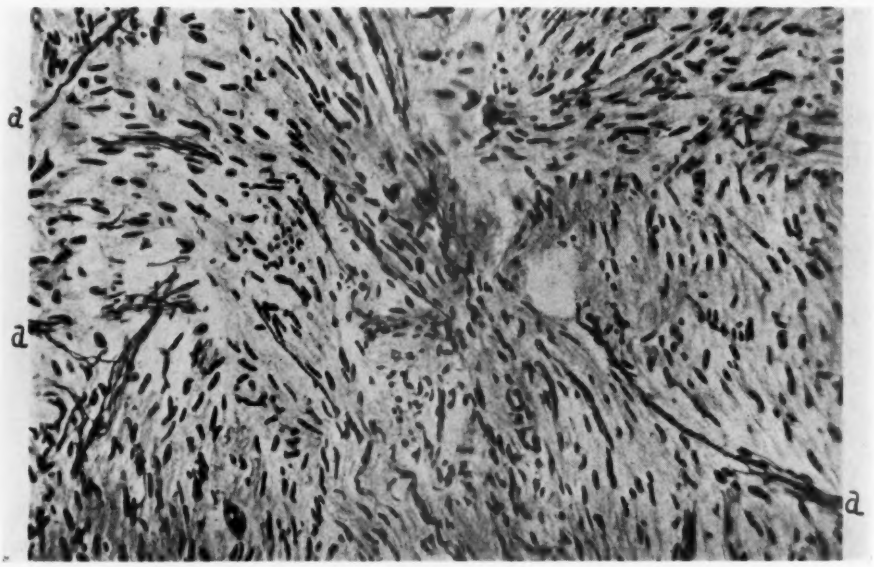

FIG. 2.—Sympathetic nerve fibers. (*a*) Invading scar formed at site of chain excision 34 days before.

pressure to preoperative levels after two months. Strands extended from the stellate scar to the vagus and the first, second, and third thoracic, and seventh cervical, nerves. Microscopic sections were made of the stellate scar and adjacent portions of strands. The scar consisted largely of connective tissue. It was traversed irregularly by sympathetic nerve fibers in groups of two or three up to ten or 15. One strand was a sympathetic nerve and probably represented the connection with the first thoracic nerve. Similar strands extended in a few cases from the lowermost thoracic ramal stumps to the scar tissue at points of excision of the chain and splanchnic nerves about the diaphragm. These offered the possibility of connections with the celiac and other plexus or with the adrenals. Grossly it was impossible by dissection to follow fibers with certainty into the ganglia or adrenals.

Microscopic sections were made of stumps of rami, scars along the field of operation, strands running from the scars and stumps toward vagus and

brachial plexus above and toward celiac plexus below, and of adrenals. They were stained for nerve fibers by the method of Bodian.[18] In the recently sympathectomized cases, small Bingner's cords of proliferating neurolemmal sheath cells were seen at the cut ends of the ramal stumps and they contained a few regenerating nerve fibers. Also scattered fibers were seen in the longitudinal scars that formed at the site of chain excision (Fig. 2). In the old experiments where the blood pressure had been restored to preoperative levels, the stumps of the rami showed an outgrowth of nerve fibers into connective tissue, sometimes with arrangement in bundles which may have penetrated scars to reach outlying ganglia. Fig. 3 shows such an outgrowth 18 months

FIG. 3.—Stump of fused gray and white rami 18 months after sympathectomy. (*a*) Proximal end, and (*b*) distal end of intercostal nerve. (*c*) Stump of cut sympathetic rami. (*d*) Scar penetrated by nerve bundles.

FIG. 4.—Nerve bundles in scar at (*d*) of Figure 3, 18 months after sympathectomy.

after sympathectomy, and Fig. 4, a large group of nerve bundles in the scar. In some instances a bulb formed at the end of the stump resembling an amputation neuroma and strands containing sympathetic nerve fibers extended on from it to adjacent scars, as shown in Fig. 5, 19 months after sympathectomy. Microscopic examination of this specimen showed preganglionic fibers growing out into the bulb and some of them on into the fibrous strands. There was no sign of outgrowing preganglionic fibers turning back in the stump with growth along the course of the postganglionic gray rami into the distal end of the intercostal nerve.

An insufficient number of microscopic examinations have been made to know the extent to which nerve fibers that have penetrated scars may have

invaded remote parts of the body. In four cases in which strands running between stellate scar and vagus were examined, nerve bundles were found in all, one of which was large. The gross evidence does not exclude the possibility that preganglionic fibers grow out to the visceral ganglia in the vagus reaching heart and lung fields and to the celiac and superior and inferior mesenteric ganglia with reëstablishment of connection with their cells. But evidence of outgrowth of fibers to reach the trunk wall and extremities is lacking, aside from possible connections with the brachial plexus. Also, if preganglionic fibers should grow into somatic nerves or into the cut ends of postganglionic fibers, and along them to their terminations, it is not known that they could function in place of postganglionic fibers. Growth to ganglion cells located along the blood vessels should lead to return of function.

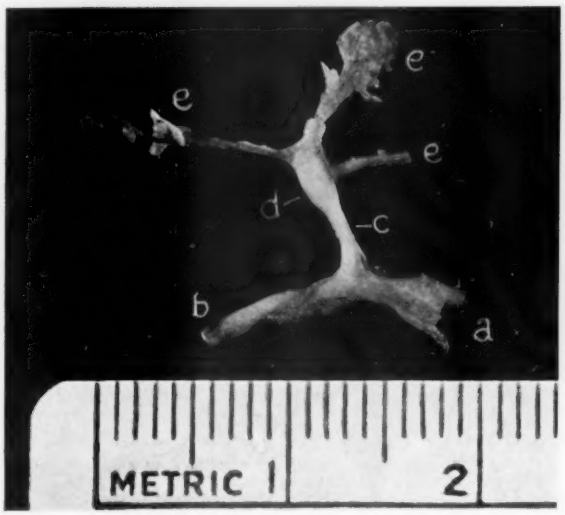

FIG. 5.—Stump of fused gray and white rami 19 months after sympathectomy. (*a*) Proximal end, and (*b*) distal end of intercostal nerve. (*c*) Stump of cut sympathetic rami. (*d*) Bulb. (*e*) Fibrous strands containing nerve fibers.

That there may be regeneration of functioning sympathetic fibers to trunk wall and extremities is supported by the following observations made on temperature control in recent and old sympathectomized animals. Three dogs, one normal, one completely sympathectomized for 38 days and showing a blood pressure of 98 Mm. of mercury against 186 Mm. of mercury before operation and one completely sympathectomized for 317 days with a blood pressure restored approximately to the preoperative level of 158 Mm. of mercury, were exposed to a temperature of −11° C. The effects on temperature are shown in Chart 9. The recently sympathectomized dog showed such prostration along with the decline in temperature that he was removed from the cold at the end of 52 minutes. Three other dogs, one normal, one sympathectomized for 80 days and showing a blood pressure of 110 Mm. of mercury against 156 Mm. of mercury before operation, and one sympathectomized for 318 days and showing a blood pressure restored to approximately

the preoperative level of 148 Mm. of mercury, were exposed to a temperature of −12° C. The more recently sympathectomized dog showed a decline of rectal temperature from 38.2° to 36° C. in 33 minutes. The old sympathectomized and the normal dogs showed slight rises of temperature during the first half hour, reaching a maximum of one degree, and normal temperatures at the end of 68 minutes.

The influence of fright and anger on pilomotor behavior of sympathectomized dogs, recent and old, was studied in only a few instances and in none was bristling of the hair observed.

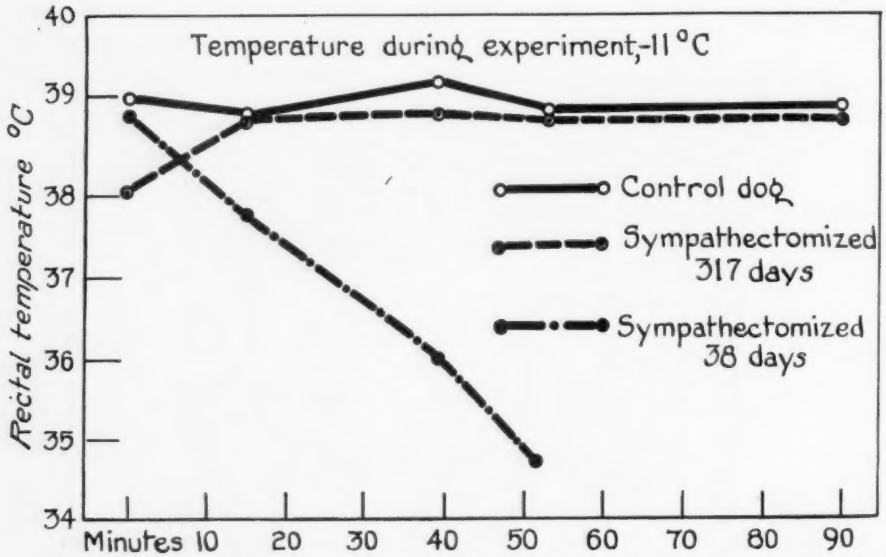

CHART 9.—Showing the rectal temperatures of dogs exposed to cold. Recently sympathectomized dog showed loss of temperature control. Remotely sympathectomized dog with recovered blood pressure showed reestablishment of control.

Retraction of the nictitating membranes paralyzed by the sympathectomy was observed within a week of the operation and progressed until the membrane was largely restored to its normal position after several months.

The real test of functional regeneration of sympathetic nerves in these experiments would be to redivide all of the rami at their points of exit from the anterior divisions of the spinal nerves to see whether or not there is again a fall in blood pressure. This was attempted in two experiments, but unfortunately the animals did not survive the difficult operative procedures.

Extrasympathetic Pathways.—The possibility of gradual activation of extrasympathetic pathways in the spinal cord and somatic nerves which normally subserve the sympathetic pathways has been considered. It has long been known that vasodilator fibers pass by way of the posterior roots to the blood vessels and the vasodilator responses obtained by sciatic and cord stimulation in some of these experiments, both recent and old, lend support to the view that they are mediated by a direct pathway from the brain stem within the somatic nervous system. There is, however, no direct evidence that vaso-

pressor pathways pass from the cord by way of the somatic nerves. Elevation of intracranial pressure, hypothalamic stimulation, and cord section and stimulation in recently sympathectomized dogs gave no blood pressure increase. This indicates that soon after the sympathectomy no functioning extrasympathetic vasopressor pathways are present.

Regeneration of Functioning Nerves to the Adrenal Glands.—According to Hollinshead,[19] the adrenal medulla of the cat is innervated directly by preganglionic fibers, as shown by degeneration of the sympathetic fibers in the medulla following preganglionic ramisection. They are derived largely from the first and second lumbar rami. A minority of the fibers are derived from the lesser splanchnics and only a very small portion from the greater splanchnics. In four completely sympathectomized dogs whose blood pressures had been restored to preoperative levels, microscopic sections of the adrenals showed a few nerve fibers in the medulla. Regeneration of physiologically active preganglionic fibers to the adrenals is thus a possibility. Since the lower thoracic and upper lumbar rami invade the scar at the sites of ganglion excision, and since strands were occasionally seen extending from this scar toward the adrenals, it is probable that the nerve fibers seen in the adrenals had regenerated along this route. The absence of any appreciable latent period before the prompt rise in blood pressure seen in the cord and hypothalamic stimulation experiments and the failure of appreciable blood pressure increase in response to sciatic stimulation and increased intracranial pressure argue against such regeneration as the sole explanation of the blood pressure recovery observed in these experiments. Even though functional regeneration to adrenal were to occur, it is problematic what rôle it would play in restoring the blood pressure to preoperative levels. The most commonly accepted view of the vascular function of normal adrenals is that of Cannon,[20] who holds that under ordinary circumstances adrenalin plays no rôle in the maintenance of the blood pressure but under emotional circumstances it may be secreted in amounts which result in blood pressure elevation. In partial ganglionic paravertebral sympathectomy, sensitization of the vessels to intravenous injections of adrenalin has been found by Freeman, Smithwick and White,[21] Ascroft[22] and others to develop within 48 hours and to persist for several months. However, in four dogs that were completely sympathectomized, intravenous injections of 1/100 cc. of 1:1,000 adrenalin per Kg. before operation, and after each operative stage, produced about the same degree of blood pressure elevation. Similar degrees of response were obtained in six dogs seven to 14 months after complete sympathectomy, when the blood pressure had been restored to preoperative levels.

Peripheral Mechanism of Pressure Control.—Following sympathectomy, there is no doubt about the gradual late return of blood pressure to the preoperative level, but it is impossible from these experiments to state how much of it is due to sympathetic nerve regeneration and how much if any to the development of a peripheral mechanism. The cord section and cord and hypothalamic stimulation experiments on recently sympathectomized dogs

failed to reveal any evidence of central vasopressor tone or control. These dogs maintained a blood pressure averaging 37 Mm. of mercury below the preoperative level, with a reduced cardiac output and without increased blood volume or blood viscosity. The experiments indicate that a peripheral mechanism is capable, soon after complete sympathectomy, of maintaining the resistance at a moderately reduced level. It has been repeatedly observed since the report of experiments by Goltz and Freusberg,[23] in 1874, that a moderate degree of tone is restored to vessels following interruption of their sympathetic nerve supply and independent of regeneration. Also, the retraction of the prolapsed nictitating membrane which usually begins within a week after the sympathectomy is evidence of the development of a local unstriped muscle contractile mechanism to replace the destroyed sympathetic mechanism. The nature of the mechanism in both cases is little understood. Ross[24] and Perlow[25] have expressed the view that the sympathetic innervation does not extend beyond the arterioles, and that the finest arterioles and capillaries are controlled entirely by chemical factors. But sympathetic nerves have been reported by Stöhr[26] and others for arterioles and to a limited extent for the capillaries. Vasodilation beyond that produced by interruption of vasoconstrictor nerves may be brought about by histamine injection or by the reactive hyperemia experiment. But nothing is known of chemical vasoconstriction of blood vessels in complete sympathectomy. Sympathetic ganglia are observed infrequently in close proximity to vessels in various parts of the body according to Kuntz.[27] Glaser[28] reported ganglion cells in the walls of the aorta and internal carotid artery. However, no recent observer, except Okamura,[29] has reported ganglion cells in the arteries of the extremities. It is not known that such ganglia exercise any function in the maintenance of vascular tone.

The rôle of such a peripheral mechanism in the sympathectomized dogs that have recovered their blood pressure is problematic. It is not demonstrated that it aids in the blood pressure restoration. An increase in peripheral resistance from a gradually increased function of such a mechanism cannot account for the observed blood pressure increases elicited by cord and hypothalamic stimulation, nor for the decline in blood pressure after cord section. These suggest rather a central vasopressor control and tone. The possibility of regeneration of preganglionic fibers across the operative scar to outlying sympathetic ganglia has to be considered in any explanation offered for the recovery of blood pressure obtained in these experiments.

Effects of Partial Sympathectomy.—Experiments were carried out to obtain information concerning the relative importance of certain portions of the paravertebral sympathetic chains in the maintenance of blood pressure and the vasopressor response to increased intracranial pressure.

Complete Heart Denervation was accomplished on four dogs in two operations, separated by intervals of 26 to 48 days. At each operation the stellate ganglion and first six sympathetic ganglia on one side of the chest were removed, and all of the thoracic branches of the vagus were divided. A slowing of the pulse rate was observed in all dogs. Blood pressures were obtained

by direct arterial puncture during periods of observation varying from 43 to 87 days. No significant alteration was noted in any of the four dogs. These animals were not subjected to intracranial pressure.

Sympathetic Heart Denervation was also effected on four dogs in two stages, separated by intervals of 32 to 40 days. At each operation the stellate and first six sympathetic ganglia were removed. A slowing of the pulse rate

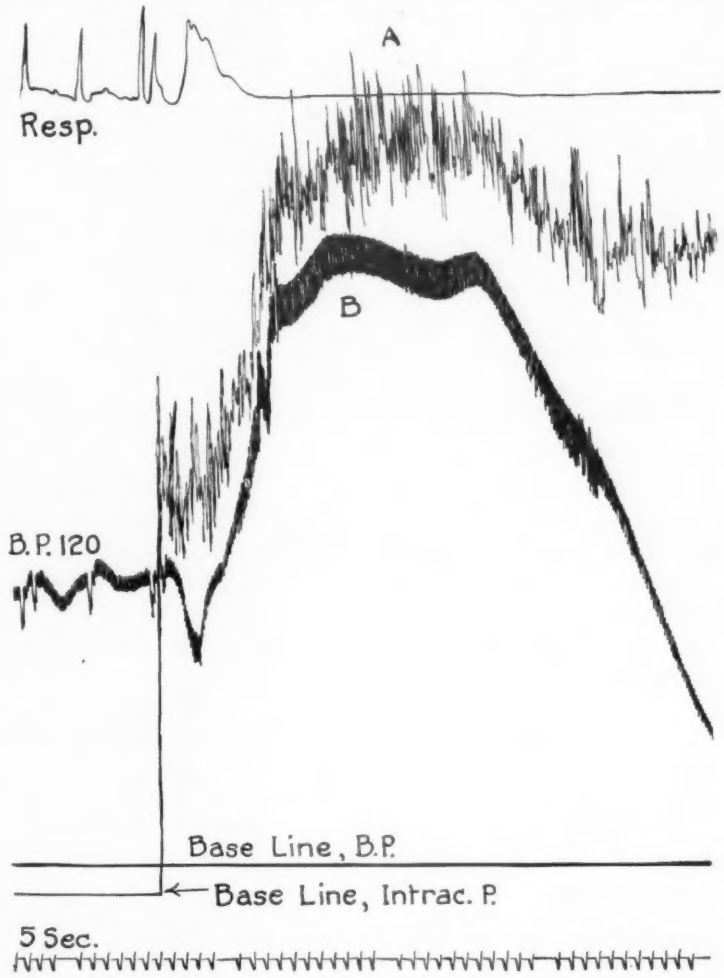

CHART 10.—Effect of increased intracranial pressure in dog after sympathetic heart denervation.

was observed. No significant alteration of blood pressure was noted in any of the four dogs during observation periods of 114 to 174 days. These animals were submitted to increased intracranial pressure. The increases above the control blood pressure were respectively 142, 96, 142, and 104 Mm. of mercury. Chart 10 shows the response of one of these dogs 108 days after the second chest operation, which is comparable with the response of a normal dog shown in Chart 6.

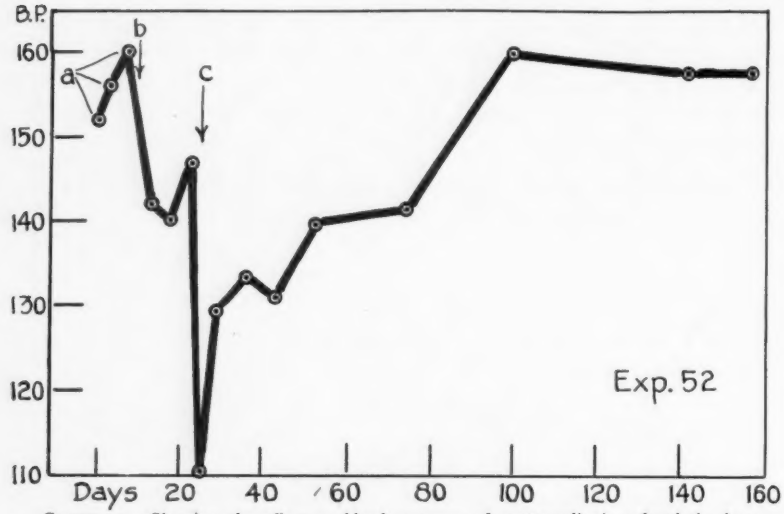

CHART 11.—Showing the effect on blood pressure of postganglionic splanchnic denervation (similar to the Peet operation). (*a*) Preoperative mean systolic blood pressure. (*b*) Right splanchnic denervation. (*c*) Left splanchnic denervation.

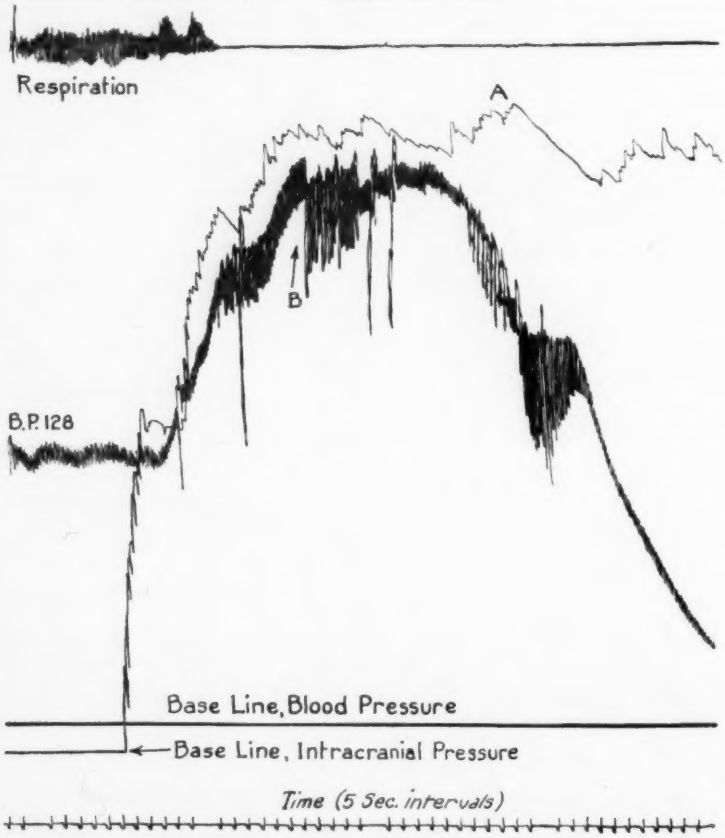

CHART 12.—Showing effect of increased intracranial pressure on blood pressure 187 days after postganglionic splanchnic denervation (lower three thoracic and 1st lumbar ganglia and splanchnic nerves).

Postganglionic Splanchnic Denervation was accomplished in two operations separated by 14 to 40 days. At each operation the twelfth rib on either side of the chest was resected to expose the origin of the greater splanchnic nerve. The sympathetic chain was removed from one or two ganglia above to one or two ganglia below the origin of the splanchnic nerves and these nerves were excised. Arterial puncture readings during periods of observation ranging from 58 to 294 days showed moderate temporary falls of blood pressure after each operation. In six to 12 weeks there was a return to the preoperative blood pressure range. Chart 11 shows a representative blood pressure curve.

Three of these dogs were sacrificed 112, 126 and 142 days after the last operation with intracranial pressure experiments. Pressure increases of 150, 164, and 134 Mm. of mercury above the control levels were reached. These readings correspond closely with the range of increase as cited above for ten normal dogs. Chart 12 illustrates the blood pressure response of one of these dogs.

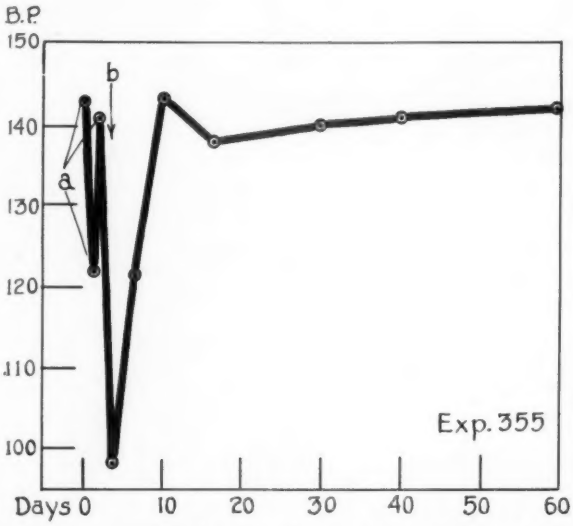

CHART 13.—Showing the effect on blood pressure of preganglionic splanchnic denervation (similar to Adson-Heuer operation). (*a*) Preoperative readings. (*b*) Rhizotomy lower six dorsal and 1st two lumbar nerves.

Preganglionic Splanchnic Area Denervation was accomplished in a single operation in which the last six thoracic and first two lumbar cord segments were exposed by laminectomy, and both anterior and posterior spinal roots divided between silver clips applied just beyond their point of junction. An immediate blood pressure lowering was noted following the operation but the animals recovered their preoperative levels in seven to 13 days. Chart 13 shows a typical blood pressure study. These dogs were sacrificed with increased intracranial pressure experiments 58 to 79 days postoperatively. The observed blood pressure increases beyond the control levels were respectively 128, 160, 146, and 162 Mm. of mercury. Chart 14 represents the tracing of one of these experiments performed 79 days after operation.

Complete heart denervation, sympathetic heart denervation, and preganglionic splanchnic denervation as described above do not appreciably alter the blood pressure level of normal dogs. Attention is directed to the fact that both pre- and postganglionic splanchnic denervation failed to alter appreciably the general vasopressor responses, as shown by the marked elevation of blood pressure elicited by greatly increasing the intracranial pressure.

Alpert, Alving and Grimson[30] produced hypertension in a previously healthy dog by partial constriction of the renal arteries according to the method of Goldblatt.[31] Complete sympathectomy was then performed. The

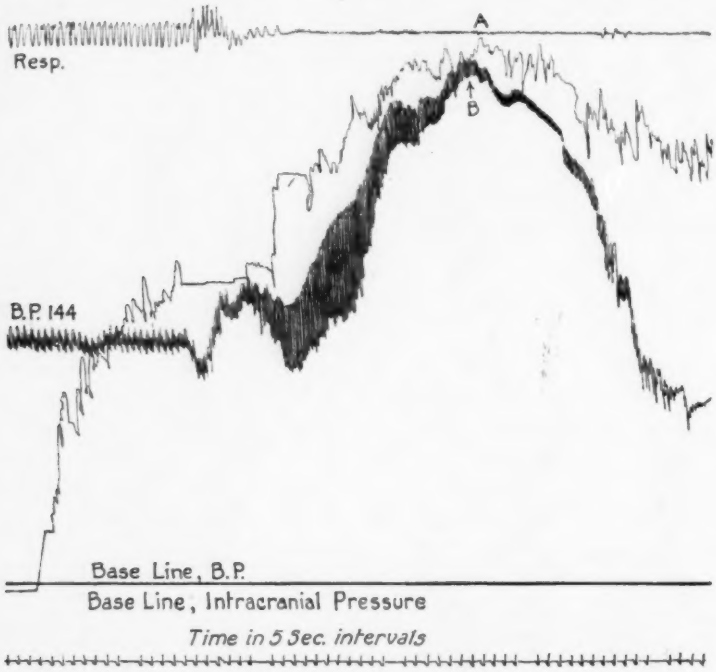

CHART 14.—Showing the effect of increased intracranial pressure 103 days after division of lower six thoracic and 1st two lumbar cord roots.

blood pressure declined slightly but remained well above the control readings. In a second dog complete sympathectomy was first performed with the usual decline in pressure. A Goldblatt clamp was applied to the left renal artery 18 days later and to the right renal artery 25 days later. An immediate hypertension then developed which persisted during the succeeding four months that the animal was under observation.

In view of the recent treatment of essential hypertension in man by preganglionic and postganglionic splanchnic denervation, it is of interest to note that the hypertension produced by the Goldblatt method in these dogs was not appreciably influenced by complete sympathectomy.

CONCLUSIONS

(1) A decline in blood pressure follows complete sympathectomy in dogs.

Restoration begins within a few weeks and reaches the preoperative level in an average time of six months.

Bradycardia and a decrease in cardiac output follow sympathectomy and persist during the stage of blood pressure recovery.

(2) The peripheral vascular resistance during the stage of lowered blood pressure following complete sympathectomy is independent of central vasopressor tone, as shown by cord section experiments, and is dependent upon an inherent vascular tone.

(3) The peripheral resistance during and after the stage of blood pressure recovery is dependent to a considerable extent upon a certain amount of reëstablished central vasomotor tone, as shown by the cord section experiments.

(4) A central nervous mechanism capable of elevating blood pressure is present during and after the stage of blood pressure recovery, as shown by cord and hypothalamus stimulation experiments. The nature of this vasoconstrictor mechanism is not well understood. Anatomic evidence indicates the possibility of preganglionic regeneration to outlying visceral sympathetic ganglia and adrenals. Gross evidence of regeneration of nerves to the trunk wall and extremities is meager.

(5) Recovery of vasoconstriction is incomplete, as judged by the response to sciatic nerve stimulation, and in one dog to increased intracranial pressure.

(6) There is a loss of the thermo-regulating mechanism of the skin in recently sympathectomized dogs and restoration of it after many months. The extent to which sympathetic regeneration or some peripheral mechanism may be responsible has not been determined.

(7) No definite evidence was obtained that there is an increase in "inherent peripheral vascular tone" synchronous with the latent restoration of blood pressure to the preoperative level.

(8) The presence of extrasympathetic vasodilator pathways in the brain stem, cord, and somatic nerves is suggested by falls of blood pressure observed on electrical stimulation of the sciatic nerve, hypothalamus, and distal-cut end of the spinal cord in dogs during the early period following complete sympathectomy.

(9) Partial sympathectomy in the form of complete and sympathetic heart denervation, and preganglionic denervation of splanchnic area did not greatly handicap the vasopressor system, as shown by their failure to lower blood pressure, or to appreciably alter the response to increased intracranial pressure. The same is true of postganglionic, splanchnic denervation except for a postoperative period of six to 12 weeks of slightly lowered blood pressure.

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STUDIES ON THE ETIOLOGY OF RENAL HYPERTENSION*

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IT HAS been known for many years that disorders of the kidneys are frequently associated with an elevation of the blood pressure. Hypertension is observed frequently in patients in whom there is long continued obstruction to the flow of urine from the kidney and the release of the obstruction usually results in a decline in the blood pressure. Fishberg[1] states that more than one-half of the patients with polycystic disease of the kidneys have a high blood pressure. Hypertension may be observed in patients with periarteritis nodosa, involving the kidney, with extensive destruction of the kidney by infection or amyloid disease or poisoning by mercury. More frequently, hypertension is encountered in patients with glomerulonephritis. Nephritic hypertension is far less frequent than so called essential hypertension. The recent experimental demonstration[2] of the fact that the artificial production of ischemia of the kidney may result in hypertension without a measurable decrease in renal function has served somewhat to break down the barrier that has separated renal and essential hypertension.

The experimental evidence that abnormalities of the kidneys may result in hypertension is convincing. A number of observers have produced hypertension by occluding the ureters. Included among these are: Rautenberg,[3] Hartwich,[4] and Harrison, Mason, Resnik and Rainey.[5] The latter authors found a well marked rise in blood pressure in nine of 13 experiments on dogs in which the ureters were ligated. Pässler and Heineke[6] were apparently the first to make an extensive study of the effects of removal of varying amounts of the kidneys on the blood pressure. Multiple operations in which, at each, the remaining portion of the kidney substance was reduced were carried out until hypertension resulted. Janeway[7] produced an elevation of the blood pressure of dogs by removal of one kidney and ligation of one branch of the opposite renal artery. Cash[8] caused a rise in both the systolic and diastolic pressures in dogs by excision of kidney tissue and ligation of renal vessels. Complete excision of one kidney did not cause a rise nor did the production of extensive renal necrosis result in hypertension. Subsequently, Cash[9] reported the results of experiments in which the renal tissue was reduced to 15 to 50 per cent of the original total and he stated: "In none of these experiments could evidence of renal insufficiency be obtained by examination of the blood for retention of urinary constituents; nor was there any striking alteration of the ability of the remaining functioning kidney tissue to excrete phenolsulphonephthalein."

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A definite rise in both the systolic and diastolic pressure was found by Cash to follow bilateral ligation of the renal arteries. On the other hand, Backmann,[10] Cash,[9] Hartwich,[4] and Harrison, Mason, Resnik and Rainey[5] have stated that an elevation of the blood pressure does not usually follow bilateral nephrectomy. Cash[9] found also that complete occlusion of all the blood vessels and the ureters of both kidneys does not usually cause a rise in blood pressure.

Several other methods have been used experimentally in producing hypertension. These include the injection of nephrotoxic substances, the application of high voltage roentgen therapy to the kidneys and the production of chronic renal venous congestion. Hartman, Bolliger and Doub,[11] by the use of roentgen therapy, caused fibrosis and vascular sclerosis of the kidneys and an associated hypertension. Pedersen[12] produced hypertension in rabbits by partially occluding the renal vein and placing a membrane around the kidney in order to prevent the development of large venous collaterals.

The interest in experimental hypertension has been given a decided impetus by the development by Goldblatt, Lynch, Hanzal and Summerville[2] of a method by which a persistent elevation of the blood pressure can be produced with greater uniformity and ease than by any means heretofore reported. The method, in brief, consists of the production of renal ischemia by partially occluding the renal arteries by silver clamps. They state: "When the constriction of both main renal arteries is made only moderately severe in the beginning, the elevation of systolic blood pressure is unaccompanied by signs of materially decreased renal function. In this respect the hypertension in these animals resembles the hypertension which is associated with benign nephrosclerosis in man." Some of the animals were observed for more than a year. Postmortem examinations of several of the animals showed definite changes in glomeruli, parenchyma and vessels of the kidneys. They state: "Gross infarction of the kidney substance was not observed in these kidneys, and microscopically massive necrosis was not present. The changes in the tissues of the animals with persistent hypertension and without signs of uremia were therefore abiotrophic rather than necrobiotic. Thus, necrosis of kidney substance was not a necessary condition for the development of elevated blood pressure in these animals. It is to those abiotrophic changes in the kidneys that the elevation of blood pressure is probably attributable because it is well known that in acute experiments clamping even of both renal vessels has little or no immediate effect on blood pressure." Goldblatt and his associates determined the systolic blood pressure by the use of the van Leersum carotid loop method. Wood and Cash[13] have produced renal ischemia by the Goldblatt method and have determined the diastolic as well as the systolic pressure by the Erlanger-Kolls-Cash sphygmographic method. A sustained rise in both the systolic and diastolic levels was observed. An extremely interesting finding which has been recorded by Goldblatt *et al.*, and Wood and Cash is that severe constriction of only one main renal artery may lead to a significant rise

in the blood pressure. There is usually a return to the preocclusion level unless the opposite artery is constricted subsequently.

Much work has been performed in the last several years in an effort to explain the mechanism by which renal disorders result in hypertension. Prinzmetal and Wilson[14] noted that anesthetization of vasomotor nerves does not release the vascular hypertonicity in hypertension. Prinzmetal, Friedman and Rosenthal,[15] and Page[16] have been unable to demonstrate pressor substances in the blood of patients with nephritis and dogs with renal hypertension. Page[17] showed that the hypertension associated with renal ischemia is not prevented by renal denervation. Goldblatt, Gross and Hanzal[18] found that splanchnic section does not prevent the elevation of blood pressure produced by renal ischemia, and does not lower the pressure in dogs with experimental renal hypertension. Goldblatt and coworkers[2] produced hypertension in an animal in which the right suprarenal body had been removed, the left splanchnic nerves had been sectioned, the left suprarenal body had been denervated and its medulla had been destroyed. Page and Sweet[19] state concerning the effects of removal of the pituitary that: "Hypophysectomy in dogs with hypertension produced by renal ischemia reduces arterial pressure to about normal levels. It appears to reduce slightly the blood pressure of normal dogs. Preliminary hypophysectomy does not prevent the rise in blood pressure established by renal ischemia, but the rise tends to be transient."

Tigerstedt and Bergman[20] observed many years ago that saline extracts of the kidneys of rabbits produce a sustained rise in blood pressure when injected into other rabbits. Harrison, Blalock and Mason[21] found that saline extracts of an ischemic kidney usually cause a greater rise in blood pressure when injected into another dog than do extracts from the opposite normal kidney. These findings were confirmed concurrently by Prinzmetal and Friedman.[22]

Since hypertension can be produced by partial constriction of the arterial supply to one kidney, without interfering with the other, it seemed important to exclude a nervous mechanism as the agency by which it is produced. Since it is impossible to be certain that an organ which remains in situ has been completely denervated, it was decided that the kidney should be transplanted to another part of the body. Such experiments constituted the first part of our study and subsequently a variety of other procedures was carried out.

Methods.—Large and medium size dogs have been used. They were fed chow which was supplemented by meat four times weekly. Water was not restricted. The animals were housed in individual cages.

The blood pressure was determined without anesthesia. A method which was utilized in all experiments consisted of introducing into the femoral artery, without making an incision, a No. 20 gauge needle which was connected to a mercury manometer. The pressure obtained in this manner corresponds fairly closely to the mean of the systolic and diastolic levels. By this method, there is very little variation in the blood pressure of normal dogs from day to day. In addition to the needle puncture method, the blood pressure of many of the dogs was determined by the van Leersum carotid loop method. Pres-

sures by the latter technic were usually determined daily for several weeks or longer preceding the operative procedures. Greater daily variations in pressure were obtained by the use of the carotid loop. The production of hypertension was usually associated with a greater rise in the pressure as determined by the loop method than by the arterial puncture procedure.

All operations which involved the exposure of the kidney or its vessels when they were in or near their normal positions were carried out under general anesthesia. Inhalation ether was used in some instances and nembutal in others. When the position of the kidney had been altered so that it was placed just beneath the skin, local anesthesia was employed in the various procedures. No evidence of pain was observed. Aseptic technic was employed in all operations.

Hypertension was produced by a number of different methods but that most commonly employed consisted of the use of the Goldblatt clamp* with which the degree of constriction of the renal artery can be varied and controlled. In some instances the clamp was applied to the renal artery of a kidney which was in its normal position, in others to the artery of a kidney which was explanted in the flank and in still others to the carotid artery leading to a kidney which had been transplanted to the neck. As has been stated, the main idea of transplantation to the neck was to be certain that complete denervation had been effected. Another reason was that it seemed to be desirable to be able to increase or decrease the amount of constriction without using general anesthesia. This can be effected without discomfort under local anesthesia when the kidney has been placed previously beneath the skin. Furthermore, the superficial position of the kidney permits of its removal under local anesthesia if it seems desirable to do so. The avoidance of general anesthesia places greater significance upon results which are obtained within the first few hours following any of these procedures. For the same reason the kidney or kidneys were explanted to the flanks in many of the experiments.

Hypertension was produced in some experiments by occlusion and division of one or both ureters. In some instances the kidney was left in its normal position while in others it was explanted to the flank. An elevation of the blood pressure was produced in a few experiments by ligation and division of the main renal arteries. Before we were aware of the Goldblatt method, hypertension was produced in several animals by gradually occluding the main renal arteries by lead bands and the arteries were subsequently ligated and divided. After the blood pressure returned to the control level following the application of a clamp to the renal artery of one kidney, the opposite normal kidney was removed in some animals and the blood pressure was followed.

The method which was used in explanting the kidney consisted simply of exposing and delivering the organ through an incision in the flank. The kidney was placed in a pocket beneath the skin. The deeper structures were loosely approximated around the pedicle. The skin incision was closed with-

* Silver clamps and instruments for their application were obtained through the courtesy of Dr. Harry Goldblatt, Cleveland, Ohio.

out drainage. Transplantation of the kidney was performed by the Carrel method. The renal artery was anastamosed to the carotid, the renal vein to the external jugular vein and the ureter was brought out through a small opening in the skin. The kidney was placed in the neck in a pocket beneath the skin.

The explantation method may be open to criticism on the grounds that this procedure alone is in some instances followed by a temporary rise in blood pressure. However, it seems likely that it is due to ischemia or at least to the same cause which results in a rise in pressure following the application of a Goldblatt clamp to the artery. The rise in pressure which may follow explantation of the kidney is usually not very great and is of short duration. Except for those experiments in which a clamp was applied to the artery at the time of the explantation of the kidney, the pressure was allowed to return to the control level before other procedures were carried out.

The methods, other than those that have been described, varied in the different types of experiments and they will be described in detail along with the results of the individual groups.

RESULTS.—(1) *Remaining Kidney Explanted to Flank—Effects of Removal under Local Anesthesia. Does an alteration in the blood pressure occur?* Ten experiments of this type were performed. As has been stated, the kidney was explanted to the flank in order that the effects of the operative procedure necessary for its removal might be reduced to a minimum. All animals except two lived four days or longer following the removal of the remaining kidney. The longest interval separating the operation and death was seven days. No significant alteration in the blood pressure was encountered in nine of the ten animals. Two of these showed a slight elevation and two a slight decline in the pressure. The remaining animal showed a rise in pressure of approximately 40 Mm. Hg. However, this dog was restless and was always shivering at the time of the determinations.

In summary, the removal of the remaining explanted kidney under local anesthesia usually caused little if any alteration in the blood pressure. The findings indicate that the maintenance of a normal blood pressure is not dependent upon the presence of kidney tissue and that the complete absence of renal tissue does not usually result in an elevation in the blood pressure.

(2) *The Effects on the Blood Pressure of the Removal of an Ischemic Explanted Kidney in Dogs with (A) Two Kidneys and (B) One Kidney. Does a fall in blood pressure occur? How long does it take the blood pressure to decline to normal level?*—Nine experiments of this type were performed. The effects on the blood pressure of unilateral renal ischemia and of subsequent removal of the kidney were studied in all experiments. In four of them, similar observations were carried out on the remaining kidney. In all instances, the blood pressure rose following the application of a Goldblatt clamp to a kidney which was explanted at the same time. The maximum rise varied from 20 to 66 Mm. Hg. when ischemia of the first kidney was produced and 28 to 88 Mm. Hg. with ischemia of the remaining kidney. General

anesthesia was administered during the explantation of the kidney and the application of the clamp. For this reason the blood pressure was not determined in most experiments during the early postoperative period. However, a definite elevation of the pressure was observed in one experiment five hours following the operation and in another at seven hours. The pressure in all instances was definitely elevated the day following the production of ischemia but the maximum rise usually occurred several days later.

Following the removal of the ischemic explanted kidney without general anesthesia, the blood pressure usually began to decline in an hour or two and in most instances approached closely the control level in six to 12 hours. It

TABLE I

EFFECTS OF REMOVAL OF ISCHEMIC EXPLANTED KIDNEY

Arterial Blood Pressure, Mm. Hg.

Dog No.	Control	One Day After Applying Clamp	Just Before Removal Kidney	7 Hours After Removal	3 Days After Removal	Control on Second Kidney	One Day After Applying Clamp	Just Before Removal Kidney	7 Hours After Removal	Days After Removal
1.....	134 (142)*	163 (170)	172 (180)	127 (150)	146 (144)	134 (138)	162 (230) 7 hrs.	177 (230)	123 (154)	137 (154) 1 day
2.....	107 (144)*	144 (166) 16 hrs.	153 (210)	119 (162)	127 (160)	120 (142)	175 (230) 5 hrs. 163	Died		
3.....	123	136	180	139 10 hrs. 123	117	112	174	160	137	147 3 days
4.....	140	157	173	143	137	143	177	198	148	129 1 day
5.....	120	139	163	125	147	128	148	158	137 3 hrs.	128 2 days
6.....	135	137	166	140 10 hrs. 121	137					
7.....	126	143	165	116	128	130	142			
8.....	118	136	150	137 13 hrs. 127	134					
9.....	150	163	170	163	148					

*The figures in parentheses in Experiments 1 and 2 are the pressures as determined by carotid loop method.

seemed quite definite in most instances that the rise in pressure following the production of ischemia was slower than the decline after the removal of the kidney. Following the removal of the second kidney, the animals did not usually live as long as did those reported in Group I in which the effects of the removal of normal kidneys were reported. Mild renal insufficiency had probably developed following the partial constriction of the renal artery in the former group.

Some of the results of these experiments are given in Table I. The findings in one experiment are shown graphically in Chart 1.

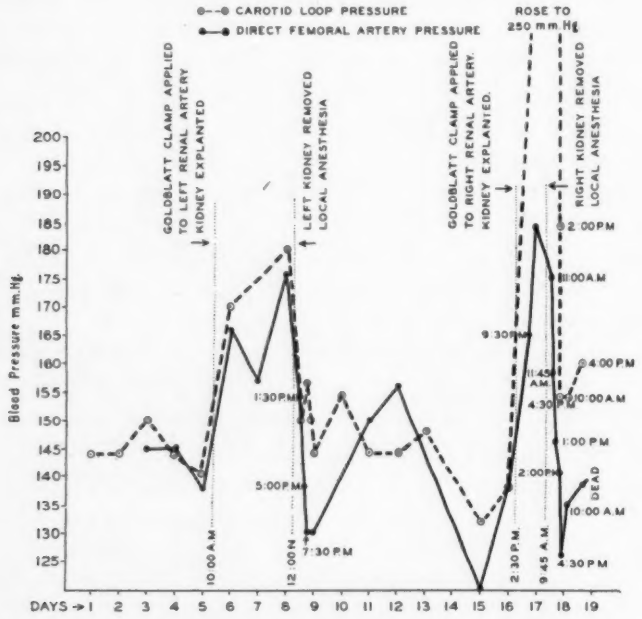

CHART 1.—The effect on the blood pressure of the removal of an ischemic explanted kidney, a normal kidney being present, and subsequently the removal of a single remaining ischemic kidney. Local anesthesia employed in removal. After sharp rises in blood pressure following constriction of the renal artery plus explantation, the pressure approached normal within seven and one-half hours after removing the first kidney, and in six and three-quarters hours following removal of the remaining kidney. It will be noted that after constricting the artery to the second kidney, the rise in blood pressure was more marked and that the loop pressure was elevated out of proportion to the femoral pressure.

In summary, the application of a Goldblatt clamp to the renal artery of one of the two kidneys, which is at the same time explanted to the flank, results in a rise in blood pressure which usually reaches its maximum in several days. However, the pressure usually begins to rise a few hours after the production of ischemia. The removal of the kidney under local anesthesia is usually followed in approximately ten hours by a return of the pressure to the control level. Similar findings were obtained when the same procedures were carried out on the opposite remaining kidney.

(3) *The Effects of Removal of a Kidney after Hydronephrosis and a Rise in Blood Pressure Have Followed Ureteral Occlusion. Does a decline in the*

blood pressure take place?—Four experiments of this type were performed. In three of these, one of the kidneys had been removed at a previous operation. At the second operation, the remaining kidney was explanted and the ureter was ligated and divided. The elevation in pressure was not as great as in the studies in which ischemia was produced by applying a clamp. The pressure rose approximately 30 Mm. Hg. in each experiment and it returned to approximately the normal level six hours following the removal of the kidney under local anesthesia. Following this latter procedure, one of the animals lived three days, one 5.5 days and the other seven days. The pressure rose somewhat subsequently in the latter animal.

One experiment was carried out in which the ureter of one of the two kidneys was ligated and divided, the kidney being left in its normal position. A moderate elevation in the blood pressure occurred several days later and the pressure returned to the control level within 24 hours following nephrectomy under general anesthesia.

In summary, the rise in blood pressure which may be associated with occlusion of a ureter is abolished by removal of the kidney. The pressure usually returns to normal in approximately six hours.

(4) *The Effects of Various Degrees of Occlusion of the Arterial Supply of the Kidneys. Under what conditions does a rise in pressure occur?*

(A) Ligation and Division of the Entire Pedicle Except the Vein. Explantation of the Kidney. Effect on Blood Pressure.—Six experiments were performed in which one of the two kidneys was freed from the surrounding structures, the entire pedicle except for the vein was doubly ligated and divided, and the kidney was placed beneath the skin in the flank. Since the kidney was freed from the surrounding structures and since the ureter as well as the arteries was divided, the kidney was entirely deprived of arterial supply. The opposite kidney was not disturbed. A significant rise in the blood pressure was not observed in any of the six experiments. The greatest increase in pressure was 15 Mm. Hg. This occurred in only one experiment and it was sustained for two days.

(B) Ligation and Division of the Entire Pedicle Except the Vein. Incisions Made in Cortex and Kidney Placed in Peritoneal Cavity.—These experiments were similar to the preceding series except that the kidney was placed in the peritoneal cavity instead of the flank and incisions were made into the cortex. Cash[9] observed a rise in blood pressure in one animal in which a kidney which was deprived of its blood supply was accidentally injured.

Four experiments were performed on dogs with only one kidney in which the procedure outlined was carried out. Three of the animals had no rise in blood pressure while it rose 25 Mm. Hg. in the fourth. Two of the animals lived two days each and two lived three days.

In three experiments, the same procedure was performed on one of the kidneys of dogs with two kidneys. None of these animals showed any appreciable alteration in the blood pressure.

(C) Ligation and Division of the Pedicle Except for the Vein and Ureter.—In all instances except two, the kidney or kidneys were explanted. In half of the experiments, the vessels were divided at the time that the kidney was explanted. In the remainder, an untied ligature was left around the vessels and they were divided subsequently under local anesthesia. The results did not seem to be affected by the time at which the occlusion was produced.

Five experiments were performed in which both kidneys were freed from surrounding structures and explanted and in which the pedicle except for the vein and ureter was divided. An elevation in pressure ranging from 16 to 40 Mm. Hg. occurred in four of the experiments and no rise was detected in the other.

In four experiments on animals with two kidneys, one of the kidneys was explanted and the arterial supply was divided. An increase in pressure of 30 Mm. Hg. occurred in one, an increase of 20 Mm. Hg. in another and no change in the pressure took place in the remaining two.

In four experiments on animals with only one kidney, explantation and division of the arterial supply were carried out. Three showed a rise in blood pressure of 20, 25 and 38 Mm. Hg. respectively.

In two experiments, the kidneys were left in situ, and the pedicle except for the vein and ureter was divided. The arterial blood pressure increased 10 Mm. Hg. in one and 35 Mm. Hg. in the other. In one experiment on a dog with two kidneys, the structures in the pedicle of one kidney except for the vein and ureter were divided and the kidney was explanted. Following a rise in the blood pressure, the kidney was removed under local anesthesia and the pressure declined. Subsequently, the arteries to the remaining kidney, except those in the ureter, were divided. The results of this experiment are given in Chart 2.

Most of these experiments differed from those described in Series A only in that the ureter was not divided in the present group. Elevations in the blood pressure were encountered much more frequently in this latter study. There was definite evidence in a number of them that the kidney was receiving an appreciable quantity of blood through the ureteral arteries. The results indicate that the pressure is more apt to rise if a small quantity of blood is reaching the kidney than if it is receiving no blood.

(D) Effects of Ligation and Division of Main Renal Artery to Each Kidney. Kidneys Left in Situ.—The renal artery was exposed extraperitoneally through the flank in the same manner as is used in the application of a Goldblatt clamp. The main artery on each side was doubly ligated and divided, the pedicle and the capsular vessels were not disturbed otherwise. Seven experiments of this type were performed. Most of the animals died on the fourth day following this procedure. All of the animals had at least a slight elevation in the blood pressure. This varied in six of them from 15 to 50 Mm. Hg.

(E) Progressive Occlusion of Renal Arteries. Destruction of Capsular Circulation.—Two experiments of this type were performed. The renal

arteries were partially constricted by lead cuffs, as we were not at that time acquainted with the use of the Goldblatt clamp. In addition, the capsule of the kidneys was stripped away. At a later time, the constriction was made more severe, and subsequently, the main arteries were doubly ligated and divided at the site of the lead cuffs. The blood pressure rose 50 Mm. Hg. in one animal and 65 Mm. Hg. in the other. The animals showed no clinical evidence of renal insufficiency despite the fact that the renal arteries were completely occluded and the capsular circulation was destroyed. Collateral circulation through the pedicle undoubtedly supplied the requirements of the

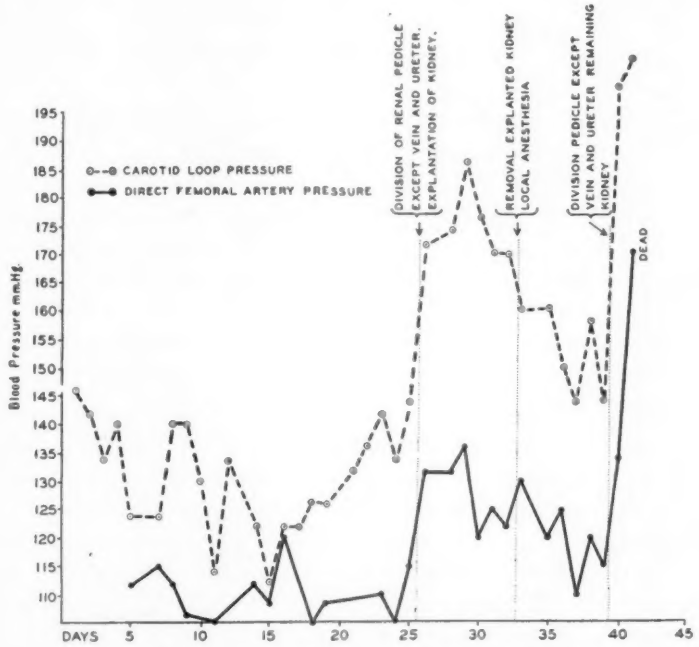

CHART 2.—The effect on the blood pressure of dividing the renal pedicle of one kidney except the vein and ureter, a normal kidney being present, and subsequently repeating the procedure on the single remaining kidney. After removing the first kidney, the blood pressure approached the control level. It is noted that the rise in blood pressure following the above procedure on the remaining kidney was more marked than when the opposite normal kidney was present; also that in general the carotid loop pressures were elevated more than femoral pressures.

kidneys. The animals were sacrificed after being observed for a year and the complete occlusion of the main vessels was verified. In this connection, it is of interest that the Goldblatt clamp frequently produces complete occlusion and at times division of the renal artery, even when the constriction produced by it was not extremely severe at the beginning.

(F) Partial Constriction of Renal Artery. Destruction of Remainder of Arterial Supply. Effect on Blood Pressure.—Five experiments were performed in which the renal artery to one of the two kidneys was partially constricted by a Goldblatt clamp and an attempt was made to destroy the remainder of the arterial supply to the kidney. These experiments were the

reverse of those in the last series in which the main artery was eventually completely occluded and the collaterals through the pedicle were not divided. The structures in the renal pedicle, except the main artery, vein and ureter, were doubly ligated and divided and the kidney was freed from the surrounding structure. As stated, this was effected on only one side and the kidney was not explanted. A temporary rise in pressure, persisting for from four to 13 days, occurred in four of the five experiments. The increases were 20, 30, 30 and 33 Mm. Hg. respectively.

In summary of this entire group of experiments, the effects on the arterial blood pressure of various degrees of occlusion of the arterial supply to the kidney have been studied. The procedures have included: (1) Complete obstruction of the arterial supply including that through the ureters; (2) obstruction of the supply except that through the ureters; (3) ligation and division of the renal arteries; (4) progressive occlusion of the renal arteries which was later made complete without interference with collateral vessels; and (5) partial occlusion of a main renal artery combined with division of the rest of the arterial supply. Significant increases in blood pressure have been noted in all groups of experiments except those in which the entire arterial supply to the kidney including that through the ureters and elsewhere has been abolished.

(5) *Goldblatt Clamp on Renal Artery of One Kidney, Normal Blood Pressure, Effects of Removal of Opposite Normal Kidney. Does a rise in blood pressure occur?*—Eight experiments of this type were performed. A Goldblatt clamp was applied to the renal artery of one kidney and a moderate degree of constriction was produced. The kidney was left in situ in two experiments and was explanted in six. A moderate elevation in the blood pressure usually followed the constriction of the artery. After the blood pressure returned to the control level, the opposite normal kidney was removed. This was followed by no alteration in the blood pressure in two experiments and by a rise in the remaining six. The maximum elevations in pressure in these experiments were 18, 26, 32, 35, 40 and 42 Mm. Hg. respectively.

These experiments were performed in an effort to determine whether or not the normal kidney influences alterations in the pressure which are associated with the partial constriction of the blood supply to the opposite kidney. The results indicate that it does.

In one experiment which does not belong strictly to this group, one of the kidneys was completely denervated by transplanting it to the neck. The carotid artery which supplied blood to the transplanted kidney was partially constricted by a Goldblatt clamp. The blood pressure rose 28 Mm. Hg. within 24 hours. The constriction of the carotid artery was lessened and the blood pressure declined 40 Mm. Hg. in the succeeding 24 hours. The normal non-transplanted kidney was then removed and the blood pressure gradually rose 40 Mm. Hg. during the succeeding seven hours.

(6) *Transplantation of One Kidney to the Neck, Opposite Kidney Re-*

moved. Effects of Reduction of Blood Supply to Transplanted Kidney on the Blood Pressure. Effects of Removal of Transplanted Kidney.—Four experiments of this type were performed. The main purpose of these studies was to test the effect of certain procedures when no doubt existed as to whether or not the kidney had been completely denervated. Following an interval of seven to ten days after the transplantation of one kidney, the other kidney was removed. On the twelfth to eighteenth day after the transplantation, partial occlusion of the carotid artery supplying the transplant was produced by the use of a Goldblatt clamp. This was followed within 24 hours in three of the four

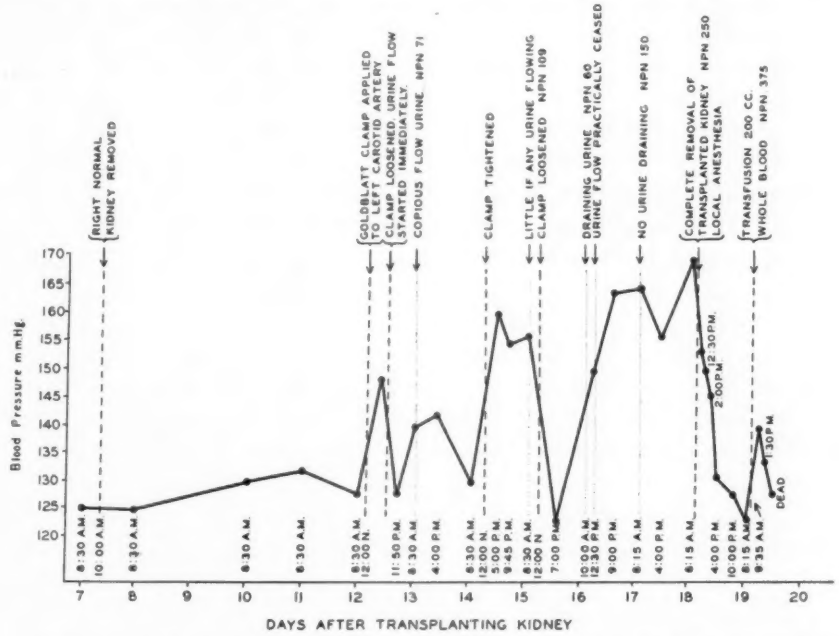

CHART 3.—Blood pressures of a dog with one kidney transplanted to the neck, the other kidney removed. The effects on the blood pressure of loosening and tightening a Goldblatt clamp applied to the carotid artery supplying the completely denervated kidney are illustrated. The blood pressure rose spontaneously on the sixteenth day, probably due to a clot at the site of the clamp. A decline in the blood pressure to normal in six and one-half hours followed the removal of the transplanted kidney.

animals by a rise in blood pressure of 16 to 29 Mm. Hg. as measured by direct femoral artery puncture. An elevation in pressure in the fourth animal was noted when the constriction was increased. The maximum increases in the blood pressure above the control levels in the four animals were 32, 40, 47 and 56 Mm. Hg. In one experiment in which the clamp was loosened after an elevation had occurred, the blood pressure returned to normal in seven hours. The blood pressure subsequently rose spontaneously to a higher level, probably due to a small clot in the artery. Removal under local anesthesia of the kidney of this animal, when the blood pressure was 45 Mm. Hg. above the control level, resulted in a gradual decline and a return to the normal in six and one-half hours. The rise in blood pressure was associated in all instances with a marked reduction in the flow of urine. Release of the constriction in

one animal, after an elevation in the pressure had occurred, resulted in a copious flow of urine. The results of one of the four experiments are pictured graphically in Chart 3.

In summary, an elevation in blood pressure was produced by partial constriction of the blood supply to the remaining kidney which had been completely denervated by transplantation to the neck. Release of the constriction or removal of the kidney resulted in a decline in the blood pressure to the normal level.

(7) *Transplantation of One Kidney to the Neck, Opposite Kidney Left in Situ. Effects of Reduction of Blood Supply to Transplanted Kidney on the Blood Pressure.*—These experiments were essentially the same as those in the preceding group except that the normal kidney was not removed. Five experiments of this type were performed. The maximum rise in blood pressure which followed the reduction in the blood supply to the transplant varied from 25 to 50 Mm. Hg. in the different experiments. In one instance, the pressure returned to the control level ten hours following the release of the constriction. In another, it declined to the control figure eight hours following the removal of the transplanted kidney. In one experiment in which the kidney received its arterial supply through a carotid artery that had been placed previously in a tube of skin, external constriction of the loop was followed by edema and superficial necrosis of the skin, and the femoral arterial pressure showed a rise of 50 Mm. Hg. When the edema subsided, the pressure returned to normal. In another experiment in which a Goldblatt clamp was used to constrict a carotid artery proximal to a van Leersum loop which contained the carotid artery supplying the transplant, the pressure in the loop as determined by needle puncture was 85 Mm. Hg. as compared with 146 Mm. Hg. in the femoral artery. Subsequent removal of the transplanted kidney resulted in a fall in the general blood pressure to normal in three hours. These observations are shown graphically in Chart 4.

(8) *Production of Hypertension by Partial Constriction of Renal Arteries to Both Kidneys Which Were Explanted. Effects on Blood Pressure of Homotransplantation of Kidney.*—Two experiments were performed in which hypertension was produced by partially constricting the arterial supply of both kidneys which were explanted. After a marked rise in pressure had taken place, one of the kidneys was removed from a normal second dog and was transplanted to the neck of the animal with hypertension. The homotransplanted kidney apparently functioned well for five days in one of the experiments and for six days in the other, but the hypertension persisted.

(9) *The Effects of Adrenalectomy on the Production of and the Persistence of Hypertension.*—Goldblatt, in unpublished observations, has found that bilateral adrenalectomy abolishes experimental hypertension. We have repeated the experiments under slightly different conditions. Five experiments were performed in which at the first operation one of the adrenal glands was removed, the corresponding kidney was explanted and its artery was partially occluded by a Goldblatt clamp. While the pressure was still elevated follow-

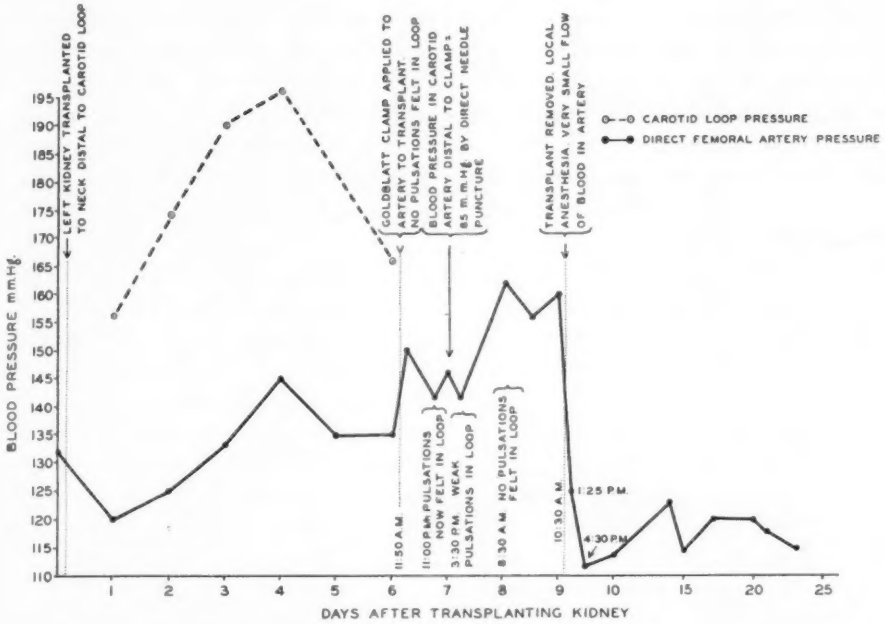

CHART 4.—Blood pressures of a dog with one kidney transplanted to the neck distal to a carotid loop, the opposite kidney left in situ. The effect on the blood pressure of constricting the carotid artery supplying the denervated kidney is shown. The blood pressure in the carotid artery distal to the constricting clamp was found to be 85 Mm. Hg. by direct needle puncture. At the same time the femoral artery pressure was 146 Mm. Hg. The blood pressure fell to normal in six hours after the transplant was removed.

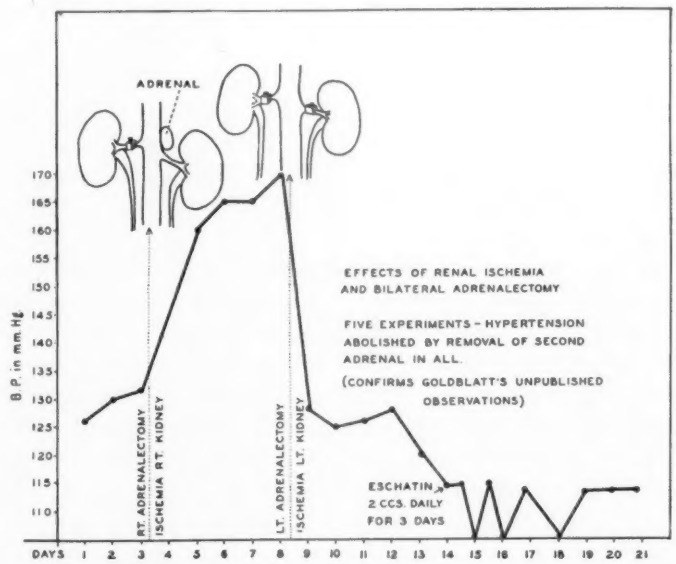

CHART 5.—Showing the effects on the blood pressure of bilateral adrenalectomy and renal ischemia.

ing this operation, the same procedure was carried out on the opposite side. The blood pressure was usually determined 16 hours subsequently and it was found in all instances to have returned to the control level. In the two instances in which it was determined five hours after the removal of the second adrenal, it had returned to normal. The animals were given sodium chloride, sodium citrate and glucose and were placed on a low protein diet. No elevation of the blood pressure occurred at any time following the removal of the second suprarenal gland. Three of the animals lived nine days or longer. The findings in one experiment are shown in Chart 5.

(10) *Effects on Experimental Hypertension of Subdiaphragmatic Splanchnic Nerve Section, Removal of Celiac and Upper Lumbar Ganglia and Partial*

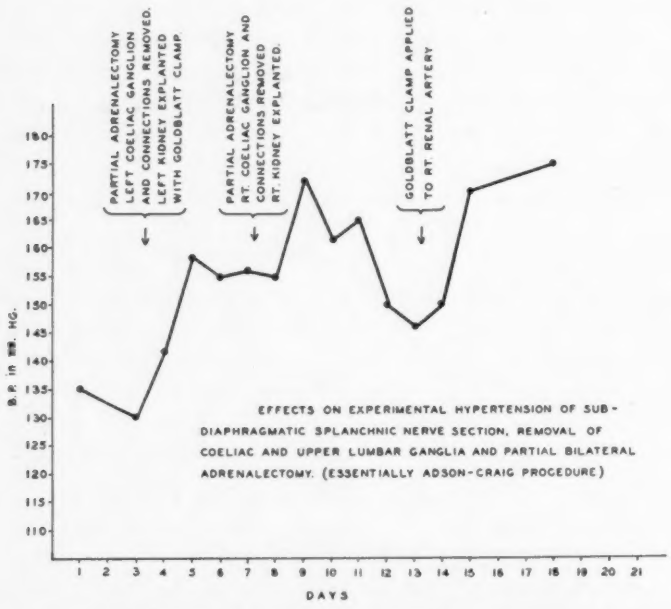

CHART 6.—Showing the effects on experimental hypertension due to results of renal ischemia of subdiaphragmatic splanchnic nerve section, removal of celiac and upper lumbar ganglia, and partial bilateral adrenalectomy.

Bilateral Adrenalectomy (essentially the Adson-Craig[23] procedure).—In three experiments, the effects on the production of hypertension of subdiaphragmatic nerve section, of removal of the celiac and upper lumbar ganglia and of partial bilateral adrenalectomy were studied. The procedure was similar to that described by Adson, Craig and Brown.[23] At the first operation, the procedure indicated was performed on the right side and the right kidney was explanted and its artery was partially occluded. A number of days later, a similar operation was performed on the left side. A definite elevation in the blood pressure occurred in the three experiments in which this was done. The maximum increases in pressure by the needle stick method were 41, 45 and 57 Mm. Hg. The results in one experiment are shown in Chart 6.

Discussion.—As has been stated, the determination of the blood pressure by puncture of the femoral artery with a needle was used in all experiments, and in addition, the carotid loop method was employed in several experiments in each group. The latter method frequently gave greater daily variations in pressure in both normal and hypertensive dogs. The alterations in pressure which were associated with the various procedures were somewhat greater when determined by the carotid loop method. If this procedure had been used throughout, it is likely that the changes in pressure in our experiments would have been more marked. As to the relative merits of the two methods, we are not competent to judge, but due to the smaller daily variations in pressure by the needle puncture method, we have more confidence in the correctness of the alterations which were detected by its use.

All of the methods for producing hypertension used in this investigation are supposedly associated with at least a temporary reduction in the arterial supply to the kidney. The total renal blood flow has not been determined following partial constriction of the main artery, total occlusion of the artery, *etc.*, but it seems certain that the flow is reduced, at least temporarily, until some of the collateral channels enlarge. Levy, Mason, Harrison and Blalock[24] have shown that ureteral occlusion is followed by a decrease in the total renal blood flow. The effects on the blood pressure of ureteral occlusion and of constriction of renal vessels are similar.

The most satisfactory method that has been developed for the production of renal hypertension is that of Goldblatt and his coworkers, which consists of partial constriction of the renal artery. We have used this method as well as several others in this study. A modification of the Goldblatt method which consists of explanting a kidney as well as constricting the renal artery has produced much more consistent elevations in pressure in our experience than any other procedure. A possible objection to explantation of the kidney is the fact that this procedure alone is very frequently followed by an elevation in the pressure for several days. However, it seems likely that this rise in pressure is dependent upon the same cause which is responsible for the elevation associated with the application of the Goldblatt clamp. At any rate, in the control studies on the effect of removal of a normal kidney under local anesthesia, sufficient time, following the explantation, was allowed for the pressure to return to the preoperative level. The explantation method has seemed to us to offer many advantages. Since general anesthesia is not necessary in the removal of an explanted kidney, the blood pressure determinations which are made during the first few hours following nephrectomy are probably of greater significance.

In this connection, it is of interest that none of our animals (Group 1) in which the remaining normal explanted kidney was removed developed a marked hypotension and only one had a significant rise in blood pressure. Harrison *et al.*[5] reported the development of marked hypotension in six of 12 animals in which bilateral nephrectomy was performed under general anesthesia. They state: "The occurrence of hypotension in most animals following

bilateral nephrectomy and in an occasional animal after ligation of both ureters can possibly be accounted for on the basis of postoperative shock and dehydration from vomiting and diarrhea. Whether the absence of renal tissue tends per se to reduce the blood pressure is still an unsettled question." Our experiments indicate very strongly that the presence of normal renal tissue is not necessary for the maintenance of a normal blood pressure, at least for the few days that dogs live after having been deprived of both kidneys.

Only one of our animals in which the remaining normal kidney was removed showed a significant elevation in the blood pressure and this animal did not appear to be relaxed and was shivering at the time of the determinations. The mechanism responsible for the rise in pressure which occurs in an occasional animal following the removal of all renal tissue is not entirely clear. Harrison *et al.*[5] state that it appears to be dependent on the central effects of deficiency of calcium ions and is brought about by the retention of phosphate and possibly also of oxalate and other substances which form un-ionized calcium salts. They further state: "The absence of an elevation of blood pressure in most nephrectomized animals in spite of marked phosphate retention can be accounted for by the simultaneous accumulation in the body of phenol-like substances which have been shown experimentally to prevent the pressor effects of phosphate."

Of greater interest in our studies were the effects of the removal of an explanted kidney, the artery of which had been partially occluded by a Goldblatt clamp with a resultant rise in the blood pressure. The superficial position of the kidney permits its painless removal without general anesthesia. By determining the blood pressure at approximately hourly intervals following the nephrectomy, a slowly progressive decline was observed with a return to the control level usually in six to ten hours. The presence or absence of the other kidney did not seem to affect the results. Almost identical findings were obtained when a hydronephrotic kidney was removed under local anesthesia. The mechanism of elevation of the blood pressure of these animals has not been elucidated but it is clear that it is abolished by removal of the kidney and that it takes a number of hours for the pressure to return to the control level.

The results of the experiments in which the effects of varying degrees of occlusion of the arterial supply to the kidney or kidneys were studied are of interest. The impairment to the renal arterial circulation produced in the different experiments included: (a) Total occlusion of all arterial supply; (b) occlusion, except for that through the ureteral vessels; (c) partial occlusion of main renal artery (Goldblatt method); (d) total occlusion of main renal artery; (e) total occlusion of main renal artery and capsular vessels; and (f) partial occlusion of the main renal artery and total occlusion of the rest of the arterial supply. An elevation in the blood pressure resulted in a high percentage of all types of experiments except those in which the kidney was entirely deprived of all blood supply. The results indicate that a diminu-

tion rather than an absence of blood supply is the important factor in the production of this type of hypertension.

It was noted in a good many of our experiments that the Goldblatt clamp eventually completely occluded the renal artery, even though the constriction was only moderately severe in the beginning, and in some instances the artery was found to be completely divided at exploration or autopsy. In this connection, it is of interest that two of our animals remained in good condition following gradually produced complete occlusion of both main renal arteries with their subsequent division and destruction of the capsular blood supply. All of the arterial blood supply to the kidneys entered through collateral vessels in the pedicle. Both of these animals developed hypertension, and were sacrificed after having been observed for one year.

An interesting, unanswered question has to do with why the blood pressure usually returns to normal following a temporary elevation for a number of days as a result of partially constricting the renal artery of one of the two kidneys. It is possible that the normal kidney takes over some of the excretory function of the ischemic one, with a resulting decline in pressure. It is unlikely that this is the explanation for it is well known that unilateral nephrectomy rarely results in an elevation in the blood pressure. It is possible that the collateral channels to the ischemic kidney increase in size and that the pressure returns to normal as the renal blood flow approaches the preoperative level. Another possibility is that the normal kidney may in some way destroy the effects of a pressor substance, if the evidence to the effect that such is formed in the ischemic kidney is correct. The experiments, in which the normal kidney was removed after the blood pressure returned to normal following the production of ischemia of the opposite kidney, were performed in an effort to throw some light on this question. A definite rise in pressure was noted in three-fourths of the experiments in which this was done. The reason for this is not apparent. Even though an elevation in the blood pressure usually follows the partial occlusion of the renal artery of one of the two kidneys or the occlusion of one of the ureters, a more marked and more lasting elevation in pressure results when the same procedures are performed on animals with only one kidney. There seems to be little doubt but that the normal kidney in some manner influences the effects of ischemia of the opposite kidney.

Additional experiments should be performed in which the pressure in the renal artery between the point of constriction and the kidney is determined. In the single experiment on a transplanted kidney in which this was done, the pressure was approximately one-half of that in the femoral artery. In another experiment on a dog with a single explanted ischemic kidney, the arterial pressure in the renal artery distal to the constriction was 85 Mm. Hg., while the femoral pressure was 170 Mm. Hg. If corroborated, they show that the production of general hypertension by the Goldblatt method is associated with renal hypotension.

In regard to the mechanism of renal hypertension, Wood and Cash[13]

state: "However, much remains to be explained concerning the physiology of renal ischemia hypertension. Apparently the occurrence of renal ischemia hypertension is not prevented by renal denervation or excision of splanchnic nerves. However, a number of our own dogs as well as some of the animals of Goldblatt and his coworkers exhibited hypertension following the partial clamping of one renal artery. This phenomenon is lacking a patent explanation if a nervous mechanism is excluded." It was with a similar thought in mind that our experiments in which the kidney was transplanted were performed, for it is the only way that one can be positive that the kidney has been completely denervated. As has been stated, a definite elevation in the blood pressure was associated with partial occlusion of the arterial supply to a kidney transplanted to the neck. The elevation disappeared when the occlusion was released or the kidney was removed. The elevations in pressure were more marked in the animals in which the normal nontransplanted kidney was removed. The experiments show conclusively that this type of hypertension may be produced when the ischemic kidney is totally devoid of nervous connections and when the opposite kidney is undisturbed.

As has been stated, Harrison, Blalock and Mason,[21] and Prinzmetal and Friedman[22] have presented evidence that extracts of ischemic kidneys contain a greater amount of pressor substances than normal kidneys. Whether these pressor substances are actually the cause of this type of hypertension is not yet certain. The possibility that the hypertension is dependent upon a diminution in the rate of formation of depressor substances has not been excluded. Page and Sweet[19] showed that hypophysectomy, in dogs with hypertension produced by renal ischemia, is followed by a reduction in the arterial pressure to the normal level. Goldblatt[25] has recently made the same observation in regard to bilateral adrenalectomy and he noted further that as long as even a small portion of the adrenal cortex remains in the body, hypertension can be produced by renal ischemia. We have confirmed Goldblatt's observations on dogs with ischemia of bilaterally explanted kidneys. Goldblatt and his associates[2] have mentioned a number of possible mechanisms whereby the blood pressure may be raised as a result of renal ischemia: (a) "Afferent impulses from the affected nerve endings in the ischemic kidneys to the sympathetic ganglia or vasomotor center may result in general vasoconstriction and consequent elevation of blood pressure." Our studies on the denervated transplanted kidneys are evidence against this possibility: (b) "Afferent impulses from the ischemic kidneys may, in some way, bring about increased output of some internal secretion which, by peripheral or central action, may effect general vasoconstriction, and thus raise the blood pressure." Again, the experiments in which the kidney was transplanted are believed to rule out the possible effects of afferent impulses. Finally: (c) "There may be an accumulation or new formation of some substance, or there may occur a disturbance of chemical equilibrium between substances present in the blood which may effect a pressor action like that of a hormone." This latter possibility seems decidedly to be the most likely one. Since the presence of the

adrenals and pituitary is necessary for the production of this type of hypertension, it is possible that the rise in pressure is due to the formation within the kidney of a substance which brings about an increased output of some internal secretion which in turn results in vasoconstriction. It seems likely that the action is peripheral since Prinzmetal and Wilson[14] found that anesthetization of vasomotor nerves does not release the vascular hypertonicity in renal hypertension. This has been confirmed by Pickering.[26] On the other hand, Dock and Rytand[27] abolished hypertension of renal origin in rats by destroying the central nervous system.

Fishberg[1] states: "Hypertension, like fever, is merely a symptom and not a disease; sometimes hypertension is produced by renal disease, but more often it is not." This was written before the work of Goldblatt and his associates appeared, but it still seems certain that all instances of hypertension are not renal in origin. For this reason and others, it is unwise to draw conclusions concerning the treatment of patients with hypertension from the experimental work that has been performed. Since hypertension can be produced by causing ischemia of the denervated transplanted kidney and since reflexes from the kidney cannot be concerned under these conditions, our results indicate that one cannot expect to relieve hypertension of this type by cutting the afferent nervous pathways from the kidneys. This confirms the findings of Page and Heuer[28] in man. As regards the more popular procedure of cutting efferent pathways, the finding, by Prinzmetal and Wilson,[14] that anesthetization of the vasomotor nerves does not release the vascular hypertonicity in renal hypertension, and particularly the observations of Goldblatt, and Gross and Hanzal,[18] that splanchnic section does not prevent the elevation of blood pressure produced by renal ischemia and does not lower the pressure in experimental renal hypertension, show very clearly that this type of hypertension is not dependent upon the integrity of these nervous pathways. Furthermore, we have found that subdiaphragmatic section of the splanchnic nerves, removal of the celiac and upper lumbar ganglia and partial bilateral adrenalectomy do not abolish experimental hypertension due to renal ischemia.

SUMMARY

A number of different types of experiments have been performed in an effort to determine the mechanism by which renal ischemia results in hypertension. The following are some of the results.

(1) When the remaining normal kidney is explanted in the flank and the blood pressure is normal, removal of this kidney under local anesthesia results in little if any alteration in the blood pressure.

(2) When hypertension is produced by partial occlusion of the renal artery of an explanted kidney, the removal of the kidney under local anesthesia usually results in a slow decline in the blood pressure, with a return to normal in six to ten hours. The rise in pressure is usually slower than the decline. Similar results were obtained in animals with only one kidney and in animals with a normal kidney in addition to the ischemic explanted one.

(3) The rise in pressure which may be associated with occlusion of a ureter is abolished by the removal of the kidney, the pressure returning to normal in approximately six hours.

(4) Various degrees of impairment of the renal arterial circulation were produced. These include: (a) Total occlusion of all arterial supply; (b) total occlusion except for that through the ureteral vessels; (c) partial occlusion of main renal artery (Goldblatt method); (d) total occlusion of main renal artery; (e) total occlusion of main renal artery and capsular vessels; and (f) partial occlusion of the main renal artery and total occlusion of the remaining arterial supply. A significant elevation in blood pressure occurred in a high percentage of all types of experiments, except those in which kidney was entirely deprived of all blood supply, including that through the ureteral vessels.

(5) When the blood pressure returned to normal following partial constriction of the artery to one kidney, removal of the opposite normal kidney usually resulted in a rise in the pressure.

(6) Partial constriction of the blood supply to the single remaining kidney which had been completely denervated by transplantation to the neck resulted in a rise in the blood pressure. Release of the constriction or removal of the kidney under local anesthesia resulted in a decline in the pressure to the normal level.

(7) Similar results were obtained with the transplanted ischemic kidney when the opposite normal kidney was not removed.

(8) Homotransplantation of a kidney to dogs with ischemia of both kidneys and hypertension did not cause a decline in the blood pressure.

(9) The observations of Goldblatt to the effect that bilateral adrenalectomy abolishes experimental renal hypertension have been confirmed.

(10) Subdiaphragmatic section of the splanchnic nerves, removal of the celiac and upper lumbar ganglia and partial bilateral adrenalectomy do not abolish or prevent hypertension due to renal ischemia.

The possible significance of these results has been discussed.

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PRODUCTION OF HYPERTENSION BY CONSTRICTING THE ARTERY OF A SINGLE TRANSPLANTED KIDNEY*

AN EXPERIMENTAL INVESTIGATION

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THE experimental work on hypertension which has been done during the past year in the surgical laboratory of the New York Hospital and Cornell Medical College has been undertaken to determine, if possible, what, if any, relationship exists between experimental hypertension and the glands of internal secretion, the nervous system, and the kidney. While none of these various phases of the work are in any sense completed, certain experiments of some interest have been carried forward sufficiently, perhaps, to warrant reporting. One of these concerns the production of hypertension in the dog by constricting the artery of a single transplanted kidney. It was thought that a nearer approach to the relation of the kidney to hypertension might be obtained if the kidney were removed from its normal position and completely isolated from its nerve supply.

METHOD.—A carotid loop (van Leersum) is made and the animal's normal blood pressure established by daily observations over a period of approximately one month. The left kidney is then removed from its normal position and transplanted intraperitoneally to the region of the groin, the renal artery and vein being anastomosed by circular suture to the femoral artery and vein. Following this procedure, a series of daily blood pressure observations are made over a period of approximately three weeks, to determine the effect of the operation upon the blood pressure. The opposite kidney is then removed and again blood pressure observations are made for approximately ten days. At the expiration of this period the femoral artery which has been anastomosed with the renal artery of the transplanted kidney is constricted by means of a Goldblatt clamp or other method. This procedure in eight animals has caused an elevation of blood pressure.

Operative Technic of Kidney Transplantation.—After dissecting free the femoral artery and vein in the groin, the peritoneal cavity is opened by an incision extending from Poupart's ligament to the costal margin. The kidney is freed and its vessels divided. By mobilizing the ureter throughout half its length, the kidney is easily brought down to the pelvis and its blood supply reestablished by end-to-end anastomosis of the renal and femoral vessels. The details of the procedure are arranged so as to reduce to a minimum the time during which the kidney is deprived of its circulation. The abdominal wound is closed over the transplanted kidney (Figs. 1 and 2).

Effects of Constricting the Artery of the Transplanted Kidney.—Dogs

* Supported by a grant from the John and Mary B. Markle Foundation.

remain in good health with a single transplanted kidney, and several of our animals have been under observation three and four months without evidence of any abnormality. Following transplantation of the kidney, there appeared a transient elevation of blood pressure of 20 Mm. Hg. in two of the animals, which may be explained by the disproportion in size between the renal and femoral veins. The blood pressure in these two animals returned to normal before they were used for further experimentation. In one animal a transient

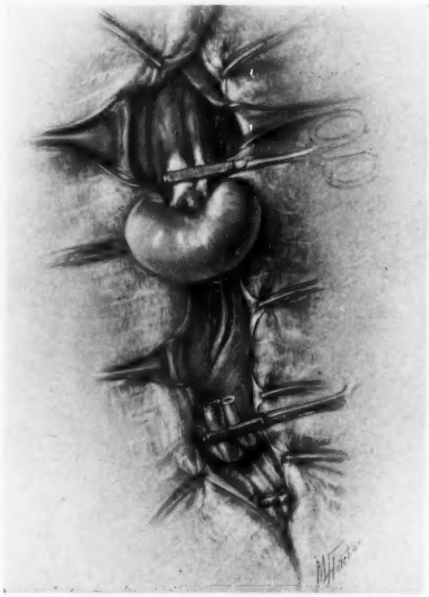


FIG. 1.—The kidney, its vessels, the ureter, and the femoral vessels dissected free preparatory to renal transplantation.

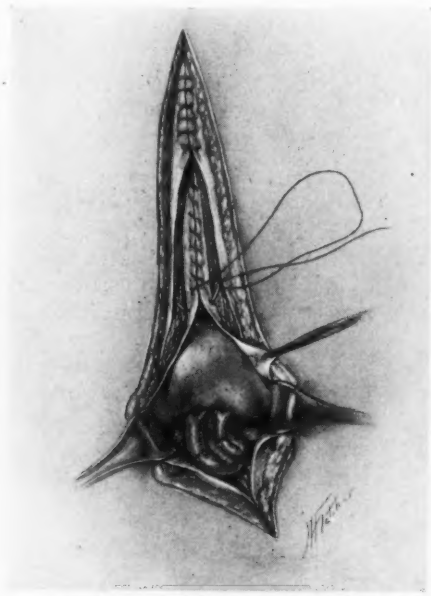


FIG. 2.—The kidney lying within the pelvis with its blood supply reestablished. Partial closure of the abdominal wound.

rise in the blood urea nitrogen followed the removal of the right kidney after the left had been transplanted. With the exception of these findings there were no changes found in the animals before the constriction of the artery of the transplanted kidney. Of the eight animals in which the artery of the transplanted kidney has been constricted, three survived and are living and five died. Brief protocols of these experiments and accompanying relevant charts are appended.

ABBREVIATED PROTOCOLS WITH RELEVANT CHARTS

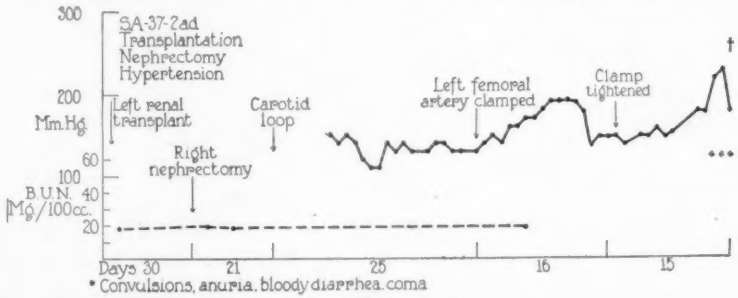
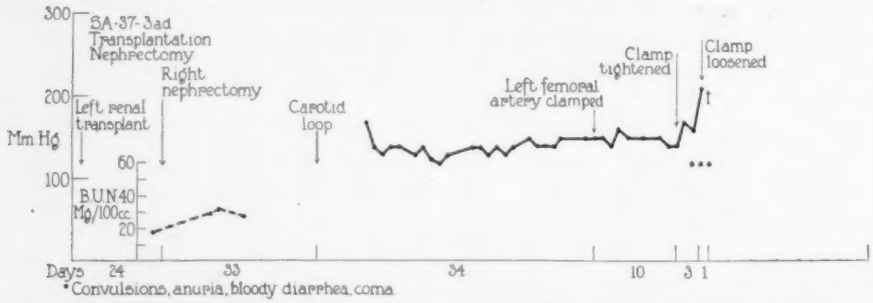
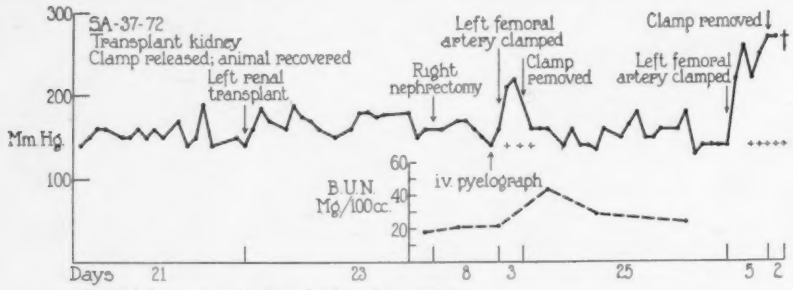


Chart 1.—Experiment I (Dog No. SA-37-2 ad): Constriction of the femoral artery; rise in blood pressure from 130 to 195 Mm. Hg.; return of blood pressure to normal; further constriction of the femoral artery with a slow rise in pressure (over a period of ten days) from 140 to 230 Mm. Hg. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



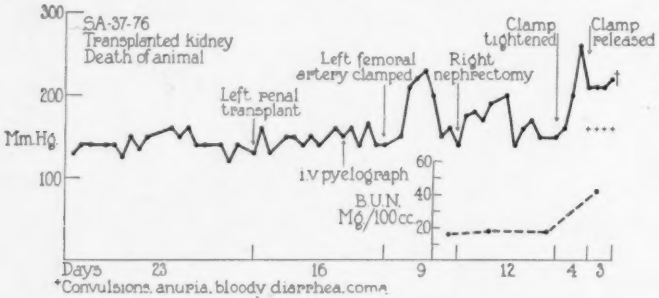
*Convulsions, anuria, bloody diarrhea, coma

Chart 2.—Experiment II (Dog No. SA-37-3ad): Constriction of the femoral artery; rise in blood pressure from 130 to 160 Mm. Hg.; return to 140 Mm. Hg.; further constriction of the artery with a rise in blood pressure from 140 to 210 Mm. Hg. Symptoms of acute intoxication necessitated release of the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



+ Convulsions, anuria, bloody diarrhea, coma.

Chart 3.—Experiment III (Dog. No. SA-37-72): Constriction of the femoral artery; rise in blood pressure from 150 to 220 Mm. Hg. Symptoms of acute intoxication; removal of clamp; complete recovery. Second constriction of the artery with rise in blood pressure from 140 to 270 Mm. Hg.; symptoms of acute intoxication; removal of the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



*Convulsions, anuria, bloody diarrhea, coma

Chart 4.—Experiment IV (Dog. No. SA-37-76): Constriction of the femoral artery; rise in blood pressure from 140 to 230 Mm. Hg.; return of blood pressure

to normal. Further constriction of artery; rise in blood pressure from 140 to 260 Mm. Hg. Symptoms of acute intoxication; clamp loosened. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*

Chart 5.—Experiment V (Dog No. SA-37-73): Constriction of femoral artery; rise in blood pressure from 140 to 240 Mm. Hg.; blood pressure maintained at 240 Mm. Hg. for eight days, then sudden fall to 130 Mm. Hg. Roentgenologic examination showed that the clamp had slipped off of the artery. Further constriction of the femoral artery; rise in blood pressure from 130 to 230 Mm. Hg.; return to 160 Mm. Hg. Animal living and well four months after transplantation of the kidney.

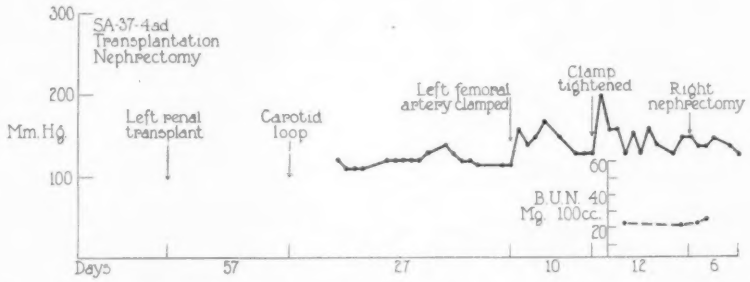


Chart 6.—Experiment VI (Dog No. SA-37-4 ad): Constriction of the femoral artery; rise in blood pressure from 120 to 170 Mm. Hg.; return of blood pressure to 130 Mm. Hg. Further constriction of the femoral artery; rise in blood pressure from 130 to 200 Mm. Hg.; return of blood pressure to 130 Mm. Hg. Animal living and well four months after transplantation of the kidney.

Chart 7.—Experiment VII (Dog No. SA-37-77): Constriction of the femoral artery; rise in blood pressure from 140 to 180 Mm. Hg.; return to 150 Mm. Hg. Further constriction of the femoral artery with rise in blood pressure from 150 to 200 Mm. Hg.; return of blood pressure to 160 Mm. Hg. Further constriction of the femoral artery with rise in blood pressure from 160 to 270 Mm. Hg. Animal blind due to bilateral detached retinae. Symptoms of acute intoxication. Animal died at operation while an attempt was being made to remove the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*

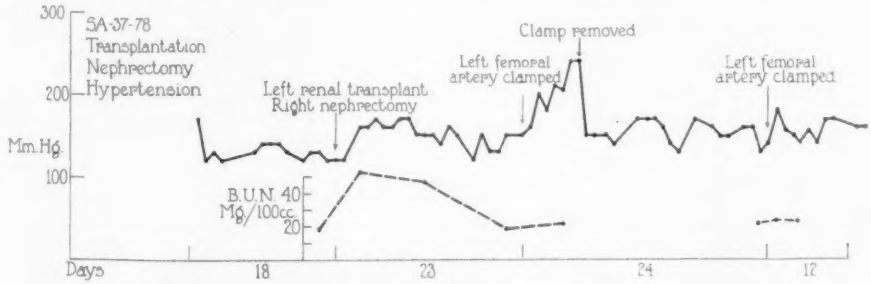


Chart 8.—Experiment VIII (Dog No. SA-37-78): Constriction of the femoral artery; rise in blood pressure from 130 to 260 Mm. Hg.; symptoms of acute intoxication necessitated the removal of the constriction; complete recovery. Further constriction of the femoral artery; rise in blood pressure from 140 to 180 Mm. Hg.; return to 150 Mm. Hg. Animal living and well three and one-half months after transplantation of the kidney.

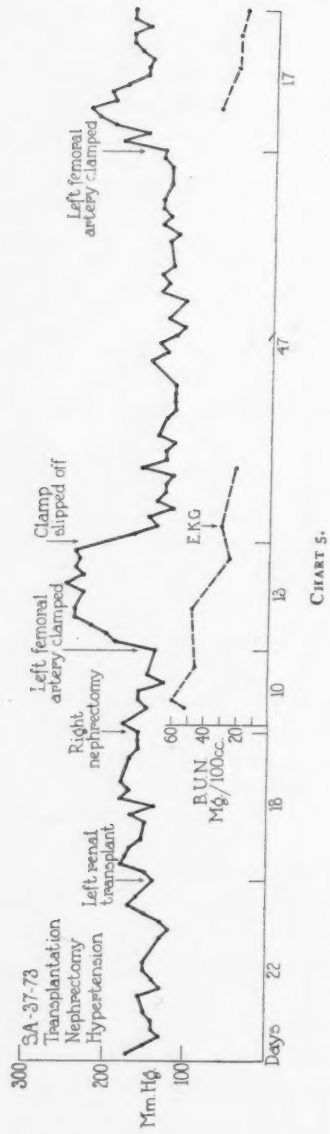


CHART 5.

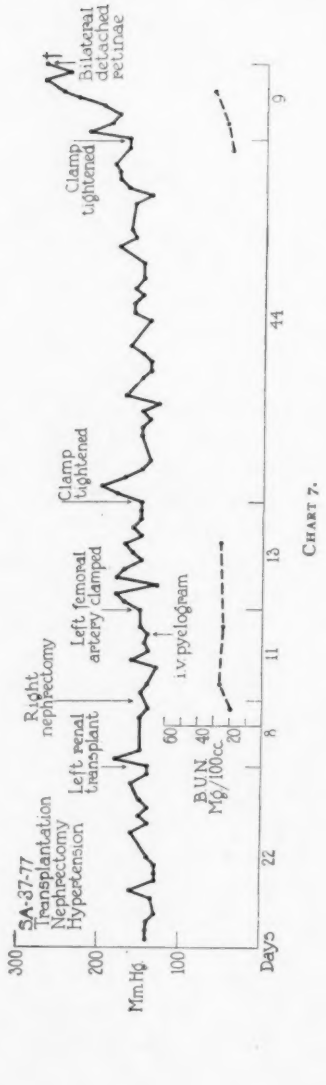


CHART 7.

* Since the initial presentation of this paper, microscopic studies of the kidneys of the animals that died following constriction of the femoral artery have been completed. The picture in each case has been one of diffuse necrosis.

No	Normal	After transpl.	1st Constriction	2nd Constriction
1		130	130 → 195 → 140	140 → 230 → †
2		130	130 → 160 → 140	140 → 210+ → †
③	150	150	150 → 220+ → 140	140 → 270+ → †
4	130	140	140 → 230 → 140	140 → 260+ → †
⑤	140	140	140 → 240• → 130	130 → 230 → 160
6		120	120 → 170 → 130	130 → 200 → 130
7	140	150	140 → 180 → 150	150 → 200 → 160
8	130	130	130 → 260+ → 140	140 → 180 → 150

• Clamp slipped + Clamp removed

CHART 9.—Composite representation of blood pressure changes produced in the preceding eight experiments.

SUMMARY.—The protocols show that hypertension may be produced in dogs by the constriction of the artery of the transplanted kidney. It will be noted that thus far we have not produced a permanent hypertension as may so readily be done by constricting both renal arteries in the dog. It is well known that it is more difficult to produce a sustained hypertension in the dog after unilateral nephrectomy; it appears even more difficult to produce a sustained hypertension after unilateral nephrectomy and renal transplantation.

DISCUSSION.—The interest in this experiment lies chiefly, perhaps, in the observation that hypertension may be produced by constricting the artery of a kidney completely isolated from its nerves. The application of Goldblatt clamps to the renal artery may not interrupt nerve impulses to and from the kidney; indeed, gross dissections of the renal artery from one week to four months after the application of Goldblatt clamps suggest that the renal nerves are not interrupted. Further work, however, on this point is in progress. Page,[1] by careful dissection, removed the renal nerves from the artery and vein and found that the exclusion of the renal nerves did not affect the level of hypertension produced by renal ischemia. Collins,[2] about a year later, employing a technic for constricting the renal artery different from that of Goldblatt, also found that denervation of the kidney is without effect on the expected rise in blood pressure. Some doubt has been expressed as to the adequacy of this method. It is asserted that following renal denervation, regeneration of the nerves may take place in three months and that these regenerated nerves may play an important rôle in the permanency of the hypertension produced by this experimental method. By experiments upon the transplanted kidney, the possible rôle of the renal nerves in hypertension may more nearly be determined. These experiments indicate that they play no part in the initiation of this type of hypertension. They suggest, however, that, because of our failure to produce a permanent hypertension, they may play a rôle in maintaining the hypertension. But this is only a supposi-

tion; and whether our failure thus far to produce a permanent hypertension by the method described is due to complete absence of the renal nerves, to some unknown abnormality of the transplanted kidney or simply to our inability thus far to secure the proper degree of arterial constriction we shall, we hope, be able to determine in the near future.

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DISCUSSIONS OF THE PAPERS BY DOCTORS PHEMISTER, GRIMSON, HEUER, GLENN AND CHILD

DR. ALFRED ADSON (Rochester, Minn.): The essayists have proved conclusively that constriction of one or both renal arteries results in increased blood pressures. By inference, one assumes that some pressor substance is not eliminated or is created during that period when the renal artery is constricted. Again by inference one has to assume that conditions may occur in the human being such as have been produced experimentally in dogs. We do know that glomerulonephritis invariably results in increased blood pressures but we still are unable to give the explanation. We also know that extensive sympathectomy fails to lower these pressures when it appears that they have resulted from renal destruction, all of which raises the question, "Is hypertension of nephritic origin the same as that of familial origin?" Thus it is obvious that physiologists as well as clinicians have innumerable problems to solve.

In our attempt to offer something towards relief of the symptoms resulting from hypertension, we have chosen patients that had a progressive disease, uncontrollable by medical measures, which appeared to be of familial origin and which was uncomplicated by other diseases. At first we were compelled to select patients for extensive sympathectomy by trial and error, but of late we have selected only those whose preoperative blood pressures could be lowered to normal readings by rest in bed, by administration of sodium amytal or by intravenous injection of pentothal sodium. We prefer not to operate upon patients who have had irreparable damage to the kidneys, heart or arterial system, since our results have shown that the advanced sclerotic, hypertensive patient will not receive any benefit from sympathectomy.

There are numerous borderline cases which one is justified in accepting for surgery but the results will not be as good as those obtained if the individual appears to present an uncomplicated vasospastic problem.

In attempting to carry out an extensive sympathectomy a number of procedures have been proposed. Our original attempt consisted of a rhizotomy which included division of the ventral roots on both sides, from the sixth thoracic to the second lumbar, thus interrupting all vasomotor impulses that might travel over the lower end of the sympathetic thoracolumbar outflow. We realized, of course, that laminectomy extensive enough to accomplish this wide sympathectomy was a formidable procedure and that sooner or later other technics effecting a similar sympathetic denervation would be introduced.

The technic that we are now employing at The Mayo Clinic, which has been used for more than two years, consists of bilateral resection of all three splanchnic nerves, a portion of the celiac ganglion and the first and second lumbar ganglions through a subdiaphragmatic, extraperitoneal approach. The

incision is very similar to a high kidney incision except that we attempt to follow anatomic lines and to resect a portion of the twelfth rib in order to secure additional exposure. The operation is divided into two stages, with an interval of about ten days between a right and a left operation.

The results of the operation depend on the degree of vasospasm present and on the extent of the disease. The younger patients, who respond favorably to preoperative studies, have obtained excellent clinical results as well as marked drops in systolic and diastolic pressures, which have remained low for intervals of more than two years. The borderline group of patients may obtain some material drop in blood pressure but do not obtain the same and continued drop that the younger patients receive who have less advanced disease. However, curiously enough, in these borderline cases there often results complete relief of symptoms, which consist of headache, cardiac consciousness, dyspnea and similar phenomena. In advanced cases, in which there are sclerotic changes, little or no result is obtained. Temporary or partial relief may be obtained but sooner or later symptoms and preoperative pressure readings return.

The postoperative sequelae of the extensive sympathectomy that we are employing at present are not contra-indications. There is an additional dryness of the skin below the first lumbar segment. There is a corresponding increase in cutaneous temperature. There is some increase in peristalsis which is of value to constipated patients and which is not troublesome enough to produce diarrhea. The extensive sympathectomy does not alter menstrual cycles or interfere with pregnancy nor does it alter potentia of the male or libido of either sex but there is a loss of ejaculatory power. Consequently, men are usually sterile following operation.

The experimental work of Phemister and Grimson does not coincide with the clinical results; patients who have undergone extensive sympathectomy, as we perform it, nearly always present marked postural influences. That is, the pressure may drop, when the patient stands, to such a degree that he may collapse. Usually this alteration of pressure adjusts itself but does not completely disappear. In a few instances we have been compelled to apply an abdominal support in order to control postural hypotension.

Dr. Edwin Beer (New York): Although the evidence is very clear that constriction of the renal circulation will produce the results that have been depicted today, it seems to me the next step in the experiment must be the determination of the pressor substance in the circulation. Within the last year, Doctor Prinzmetal, who was quoted by one of the readers today, has called attention to the fact that by animal experimentation on the denervated ear of the rabbit, he has been able to show in the circulating blood in hypertensive seizures in a case of pheochromocytoma the pressor substance, and he has been able to counteract that effect by the use of its antagonist ergotamine. It seems to me the most important thing to determine in these experiments is whether the pressor substance is circulating in the blood following constriction of the renal artery, and what the pressor substance is.

Dr. Alfred Blalock (Nashville, Tenn.) closing: An important step would seem to be to prove whether or not there is any relationship between the type of hypertension produced by causing renal ischemia and that which is encountered in any of the hypertensive states in man. That is probably going to be a very difficult undertaking.

I should like to say that we draw no conclusions concerning the treatment of hypertension in man from the experiments that have been reported.

DR. GEORGE J. HEUER (New York) closing: I agree with Doctor Blalock that it is desirable if possible to relate the hypertension produced in dogs by the Goldblatt method with the hypertension as it occurs in the human subject.

We, too, have been interested in this relationship. In experimental hypertension it has been shown by the experiments of Phemister and Grimson, and by destruction of the spinal cord as done by ourselves, that no method of procedure thus far directed at the sympathetic nerves will serve permanently to lower the blood pressure in hypertension produced by the Goldblatt method.

The human subject with hypertension appears to react to bilateral splanchnicectomy in much the same way as does the dog with experimental hypertension. In a small group of cases of hypertension in which we have performed bilateral splanchnicectomy and which have been observed over periods of more than a year, the blood pressure reduction as a result of the operation has returned to or now exceeds its previous level. Similar experiences are reported in the literature.

In a group of 25 cases of hypertension treated by rhizotomy, 15 have been followed for periods from one and one-half to three years. In these the results with respect to the blood pressure are as follows: In three out of six cases of mild hypertension, three out of six cases of severe hypertension, and one out of five cases of malignant hypertension, the blood pressure has been greatly reduced and shows no tendency to rise after one to three years. In three additional cases the blood pressure was reduced and showed no tendency to rise during the period of observation, but the patients died from nine to 16 months after operation.

In three cases of mild hypertension, one case of severe hypertension and one case of malignant hypertension, the blood pressure reduction resulting from the operation has shown a tendency to rise anywhere from three to 15 months after operation, and now after one and one-half to three years, has risen to its preoperative level in three cases, but is still considerably below its preoperative level in two cases. This experience, you will observe, is not exactly similar to that in experimental hypertension in animals. In one case of hypertension, I performed a bilateral renal denervation which did not affect the blood pressure. This observation is similar to observations made in dogs. In one case of rapidly advancing malignant hypertension, symptoms of complete transverse myelitis appeared before the anterior roots were divided. The blood pressure remained normal for one and one-half years. Recently, however, at the expiration of two years, his blood pressure is showing, I think, a tendency to rise.

This is the experience which I have had to date with hypertension in the human subject. While in some respects it resembles the experience in dogs, in other respects it does not. Such as it is, it suggests to me that there is a similarity between the hypertension produced in dogs by the Goldblatt method and essential hypertension as seen in the human subject.

EPINEPHRINE HYPERTENSION

THE EFFECT OF THE CONTINUOUS INTRAVENOUS INJECTION OF EPINEPHRINE ON THE BLOOD PRESSURE

AN EXPERIMENTAL INVESTIGATION*

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WITHIN recent years surgeons have become interested in the possibility of treating hypertension by various operative procedures. The methods employed have been designed to accomplish a removal of vasomotor control over a large distribution of the vascular bed and a diminution in the rate of secretion of epinephrine. Varying degrees of success have been reported and it seems to have been established that the operations of sphlanchnicotomy, or bilateral division of the anterior roots of the sixth dorsal to the second lumbar spinal nerves will produce, quite regularly, a decrease in the systolic and diastolic blood pressure in essential hypertension and that this improvement may be maintained for from one to two years (Heuer,[1] 1936, and Adson,[2] 1936). The recent discovery by Goldblatt, Lynch, Hanzal, and Summerville[3] that a long continued hypertension can be produced in dogs by the application of a specially devised clamp which constricts the renal arteries has made the problem susceptible of experimental approach. The demonstration that this hypertension may occur even if the kidneys have been previously denervated (Irvine Page[4]) or the splanchnic nerves excised (Goldblatt[5]) indicates that a humoral mechanism is involved. A rational basis for splanchnicectomy and allied procedures would seem to depend on the possibility that the unknown chemical implicated in hypertension acts on the vasoconstrictor centers. Palliation through removal of normal vasoconstrictor impulses would be expected to be short-lived since Phemister and Grimson[6] found that the fall of blood pressure which follows complete sympathectomy in the dog persists for only a short period and in all cases there is a return to normal within a year.

The operations designed to decrease the secretion of epinephrine have consisted in bilateral adrenal denervation and partial or subtotal adrenalectomy. Here also favorable results have been reported by Crile[7] and DeCourcy.[8] It should be kept in mind, in this connection, that the adrenal cortex is essential to life and that it is damaged more or less severely in the operations designed to lessen the function of the adrenal medulla. To

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what extent the effects produced by these operations can be attributed to cortical damage cannot be determined by the clinical data. While it is probable that the output of epinephrine is reduced, a more thorough procedure has been found necessary to abolish its secretion in the experimental animal (Rogoff,[9] 1936).

The theory that various forms of hypertension might be caused by the excessive production of epinephrine was advanced shortly after the discovery of the pressor effect of adrenal gland extracts by Oliver and Schaefer[10] and the isolation of epinephrine from the suprarenal medulla by Abel. In the intervening years considerable support for this theory has accumulated as a result of clinical observation and animal experiments. This evidence may be classified under the following general groups: (A) Experimental data indicating a small but continuous secretion of epinephrine which plays a rôle in the maintenance of the normal blood pressure; (B) data indicating the presence of excessive amounts of epinephrine or other pressor substances in the blood stream of patients with high blood pressure; and, (C) the observation of cases of hypertension in association with tumors or hyperplasia of the adrenal glands.

Qualified opinion with respect to the function of the adrenal medulla is still far from agreement, and this in spite of an enormous amount of careful experimental work. Two general conceptions have arisen: The tonus theory and the emergency theory. The tonus theory assumes that there is a steady and constant liberation of epinephrine in small amounts at all times and in all physiologic states and that the quantity thus liberated is sufficient to maintain normal arterial tone by establishing a state of receptivity by the stimulation of the sympathetics. The emergency theory, presented by Cannon, in 1914, holds that while the constant secretion may be negligible in effect, under circumstances of great emotional stress, pain, or asphyxia there is a marked augmentation of secretion. This augmentation is of such a degree that effects are produced which muster the resources of the individual in such a way as to best meet the necessities of flight, combat, or pursuit. Cannon states: "The cessation of activities of the alimentary canal; the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart, the central nervous system, and at critical moments, the skeletal muscles as well; the increased cardiac vigor; the quick abolition of effects of muscular fatigue, the mobilizing of energy-giving sugar in the circulation—these are the changes which occur when fear or rage or pain causes the suprarenal glands to pour forth an excessive secretion." Objections to both of these theories have been raised on the basis of experimental evidence. Rogoff and Stewart have developed a biologic method for determining, quantitatively, the output of epinephrine from the adrenal glands and this has revealed in the dog a small but continuous secretion which can be greatly increased by stimulation of the sympathetic nerves going to the glands. Using this method Rogoff has found that neither as-

phyxia nor stimulation of the central sciatic causes an increased secretion of epinephrine. The increase in the rate of the denervated heart which Cannon found to result from these procedures must be due to something other than epinephrine since Rogoff found such an increase in heart rate to occur when the blood from the adrenal veins was not allowed to return to the circulation but was being collected in a beaker for examination. An objection to the emergency theory may be stated also from the standpoint of clinical observation. In those cases of chromaffin tumor associated with paroxysmal hypertension and where it seems highly probable that occasional outbursts of epinephrine into the circulation are responsible for the symptoms, the effect of the sudden increase in epinephrine secretion is not such as to increase the ability of the patient to meet an emergency, but rather quite the reverse. For a varying period of time the patient is partially or completely incapacitated.

A serious objection to the tonus theory arises from the fact that cats, dogs, and monkeys have been found to live indefinitely, in good health, after removal of one adrenal and complete denervation of the other, an operation which reduces the output of epinephrine to an undetectable amount. Furthermore, dogs and cats have been kept alive, and in good condition, after bilateral adrenalectomy by the administration of cortical extracts free from epinephrine. We are reluctant, however, to conclude from this evidence that the adrenal medulla and its product epinephrine have no significant function. It must be admitted that there is a considerable amount of extra adrenal chromaffin tissue and the demonstration of epinephrine in tumors arising from this tissue suggests that it has a functional capacity similar to that in the adrenal medulla. Further objection to the view that a small but continuous secretion of epinephrine plays a rôle in the maintenance of the normal blood pressure has been found in the work of Moore and Purinton,[11] 1900, and of Hoskins and McClure,[12] 1912, both of whom reported that minimum effective doses of epinephrine caused a fall rather than an increase in blood pressure. Hoskins and McClure also reported that the minimum quantity of epinephrine in the blood required to raise the blood pressure was more than sufficient to inhibit the motility of the gastro-intestinal tract. Both of these objections, however, have been made untenable by the recent experiments of C. A. Dragstedt, Wightman, and Huffman,[13] 1928, and C. A. Dragstedt and Huffman,[14] 1928. These investigators found that the depressor effect of small doses of epinephrine was due to the anesthesia and that if measurements were made on the undrugged, unanesthetized dog, the minimal effective dose of epinephrine on sustained intravenous administration caused an increase in blood pressure without inhibition of the motility of the gastro-intestinal tract. A pressor response was obtained with doses of epinephrine varying from 0.0002 to 0.0004 mg. per kilo. of body weight per minute. This is but slightly greater than the average output of epinephrine from the adrenals which Stewart and Rogoff,[15] 1920, estimated to be 0.00022 mg. per kilo. per minute in the

dog. In recent experiments C. A. Dragstedt,[16] 1928, found that compatible suprarenal vein blood collected from one dog and reinjected into a second unanesthetized dog at the rate at which it was collected, produced a slight rise in blood pressure which was not secured by the injection of systemic blood. He concluded that the adrenals normally and constantly secrete epinephrine in amounts sufficient to modify the vascular bed and that a slight augmentation of secretion might easily produce hemodynamic effects. These observations, it seems to us, provide very strong support to the tonus theory of medulliadrenal function and at the same time remove some of the more formidable objections to the view that a hypersecretion of epinephrine may be the cause of hypertension.

Attempts to demonstrate the presence of pressor substances in the blood of patients with high blood pressure have led to contradictory results. Using a strip of surviving artery as a test object, Janeway and Park[17] were unable to find epinephrine in the systemic blood of patients with hypertension. A similar result was reported by Huelse.[18] Schur and Wiesel[19] reported that the serum of hypertension subjects would cause dilation of the pupil of the enucleated frog's eye but O'Connor[20] concluded that this reaction was not specific for epinephrine but was produced by substances formed during the coagulation of blood. Bohn[21] found that alcoholic extracts of the blood from patients with malignant hypertension and with eclampsia gravidarum caused a marked rise in the blood pressure of cats on intravenous injection. Similar extracts of the blood of normal people produced no effect. Konschegg[22] treated an alcoholic extract of dried blood with acid and found that the product behaved like epinephrine on a surviving strip of rabbit's intestine; namely, it stopped or inhibited the contractions. He stated that such an extract was active in 1 to 6,000 dilution when prepared from normal blood, but in 1 to 30,000 dilution when prepared from the blood of hypertensive subjects. The activity of the extract was greater the higher the blood pressure of the subject from whose blood the extract was prepared. Irvine Page,[23] on the other hand, obtained pressor substances in alcoholic extracts of blood and other body fluids but found no increased amount in cases of hypertension of varied pathogenesis such as nephritic hypertension, essential hypertension, malignant hypertension, eclampsia, and pituitary basophilism. It is quite apparent from this brief and incomplete survey that the existence of hyperadrenalemia in hypertension has not been established by the direct method of examination of the blood. It must be admitted, however, that exceedingly small amounts of epinephrine are all that are required and that methods for its detection in body fluids are exceedingly difficult.

Perhaps the best evidence suggesting the possibility of hyperfunction of the adrenal medulla as the etiologic factor in hypertension is the relatively recent delineation of the symptom complex often seen in patients with chromaffin cell tumors. Since 1922, when Labbe, Tinel, and Doumer[24] first described a chromaffin cell tumor of the adrenal medulla associated with

hypertension, a considerable number of such cases have been reported. The literature has been thoroughly reviewed by Coller, Field, and Durant[25] and Belt and Powell.[26] These tumors have been called peritheliomata or pheochromocytomata and when they arise from the extramedullary chromaffin tissue, paragangliomata. Patients with such tumors have been found to display a paroxysmal hypertension together with other symptoms such as pallor, profuse sweating, dyspnea, headache, precordial oppression, bradycardia, nausea and vomiting. The origin of these tumors from the adrenal medulla, their histologic appearance and brown staining after chromate fixation, and the similarity of the symptoms of the paroxysmal attack with those produced by an injection of adrenalin suggest that a sudden excretion of adrenalin is the proximal cause of the hypertension. This is supported by the demonstration of epinephrine in the tumor tissue. Kelly, Piper, Wilder, and Walters[27] estimate that the tumor they reported contained 300 mg. of epinephrine and Belt and Powell[26] reported 2 Gm. of epinephrine per 100 Gm. of tumor in their specimen. As further evidence that hyperadrenalemia is the cause of the systemic symptoms, massage of such a tumor through the abdominal wall (Pincoffs'[28] patient) or the assumption of certain positions (Porter and Porter,[29] and Belt and Powell,[26] reproduced the symptom complex. Finally the successful removal of such tumors has been found to abolish further attacks. The detection of epinephrine in the blood of these patients during an attack is desirable and should be feasible. At the present time this evidence is lacking but it is probable that an adequate test with the best available technic has not yet been made. Such evidence would also provide information concerning the concentration of epinephrine in the blood required to produce such a symptom complex. The paroxysmal nature of the outburst of epinephrine is also a problem of great interest, and is a feature of the disease that should be stressed. In practically all cases the attacks have been of relatively brief duration and have been succeeded by long periods of freedom when the blood pressure has remained within normal limits. A persistent elevation of blood pressure in the presence of such tumors has not been so clearly defined. Indeed, it is doubtful if the patient could survive the persistence of so serious an attack.

The fairly regular association of hypertension as a part of the suprarenal cortical syndrome outlined by Gallais,[30] Krabbe,[31] and recently by Walters, Wilder, and Kepler[32] has forced consideration of the cortex of the adrenals in the pathogenesis of hypertension. Indeed, from the clinical and pathologic standpoint there is better evidence that hyperfunction of the cortex rather than the medulla may play a rôle in essential, as opposed to paroxysmal, hypertension. A more or less persistent and constant hypertension was observed by Walters, Wilder, and Kepler in cases of adenocarcinoma of the adrenal of cortical origin, and the blood pressure returned to normal following removal of the tumor only to reach a high level once more when the carcinoma recurred.

It has been amply demonstrated that an intravenous injection of epinephrine will produce a transient but very marked increase in blood pressure. The present experiments were designed to determine if this hypertension might be indefinitely maintained by the sustained continuous injection of varying amounts of epinephrine.

EXPERIMENTAL PROCEDURE.—Two types of experiment were undertaken. In the first adult dogs were given morphine and placed in a comfortable position on the table. Under local novocain anesthesia the femoral artery was isolated and cannulated for the measurement of blood pressure and the femoral vein prepared for the injection of epinephrine. By this method it was seldom possible to continue the experiment more than a few hours because of clotting so that recourse was had to a somewhat more complicated procedure. Healthy male dogs, weighing from 10 to 12 Kg., were selected and kept under observation with occasional handling for a period of at least four weeks. Control tracings of the blood pressure were taken during this time by the direct method. A No. 18 gauge needle was introduced into the femoral artery after novocain infiltration and this was connected with a mercury manometer in the usual manner. After from two to five satisfactory control measurements had been secured, the animals were prepared for the continuous injection of epinephrine in the following manner: Under morphine and local anesthesia and with aseptic precautions the external jugular vein was isolated through a small incision. A segment of exceedingly fine rubber tubing, as described by Jacobs,[33] was then introduced into the vein through an hypodermic needle and the outer portion led through the skin and connected by means of pressure tubing with the injection apparatus. This consisted of a 100 cc. glass syringe whose plunger was driven by a slowly revolving motor driven screw. The pump was calibrated to deliver ⅛ cc. of fluid per minute. To give the animals complete freedom of motion in their cages the method described by Jacobs[33] was employed. Epinephrine hydrochloride solution of 1 to 1,000 dilution was used. This was diluted with distilled water or 0.9 NaCl and fresh solutions were prepared every 14 hours. The dose of epinephrine varied between 0.0009 and 0.003 mg. per Kg. of body weight per minute, with the majority of animals receiving 0.002 mg. The blood pressure was determined daily by means of a tracing as previously described. The results are described in detail in the protocols. Satisfactory experiments were secured with 15 animals and a continuous injection of epinephrine maintained for periods of 100 to 336 hours. The method used permitted sufficient freedom so that the animal could be removed from the cage, placed on a table, and the blood pressure recorded without disturbing the injection.

PROTOCOLS

Animal No. 1.—Male. Wt. 9.5 Kg. Control blood pressure measurements were made by the direct method with the following results: 3-15-35, 106 Mm.; 3-18-35, 126 Mm.; 3-20-35, 126 Mm.; 3-22-35, 98 Mm.; and 3-25-35, 104 Mm. On 4-13-35 the continuous intravenous injection of epinephrine at the rate of 0.0009 mg. per Kg. of body weight per minute was started. The injection continued satisfactorily for 96 hours and during this time the following symptoms were manifested:

Panting, anorexia, vomiting, and increased thirst. The general condition, however, remained good. The rate of injection was then increased to 0.0015 mg. of epinephrine per Kg. per minute. On 4-18-35 or 120 hours after the beginning of the injection the systolic pressure measured 166 Mm. of Hg. A day later the rubber tube came out of the jugular vein and the experiment was discontinued.

Animal No. 2.—Male. Wt. 9.0 Kg. Three control measurements of the systolic blood pressure were made, the highest of which was 100 Mm. The urine contained no sugar. On 5-9-35 the intravenous injection of epinephrine at the rate of 0.002 mg. per Kg. per minute was started. The animal soon became sick, depressed, and vomited practically everything taken by mouth. Later all food was refused. On 5-11-35, 48 hours after the beginning of the injection, the systolic pressure measured 157 Mm. The injection was now stopped momentarily and the pressure fell promptly to 127 Mm. When the injection was resumed the pressure rose rapidly to 173 Mm. On 5-16-35, 168 hours after the beginning of the injection, the systolic pressure measured 143 Mm. and when the injection was temporarily stopped it fell to 113 Mm. On 5-20-35, 264 hours after the beginning of the injection, the pressure measured 150 Mm., and when the injection was stopped it fell to 121 Mm. On 5-22-35 the tubing came out of the jugular vein and the injection was discontinued. The systolic pressure was 116 Mm. and the next day measured 115 Mm. With the cessation of the injection the animal began to eat and in a short time appeared entirely normal. A 24-hour specimen of urine collected 36 hours after the injection began contained 1.1 Gm. of sugar, but all subsequent specimens were sugar-free. At the 48th hour the blood sugar was 102 mg., at the 120th hour 99 mg., at the 192nd hour 95 mg., at the 264th hour 106 mg., and at the 312th hour or after the injection stopped it fell to 77 mg. and was still at that level on the following day.

Animal No. 3.—Male. Wt. 15 Kg. Control measurements of the systolic pressure yielded data as follows: On 4-2-35, 130 Mm.; on 4-5-35, 128 Mm.; and on 4-16-35, 130 Mm. The urine was sugar-free. The intravenous injection of epinephrine at the rate of 0.001 mg. per Kg. per minute was started on 4-23-35. Twenty-four hours later the systolic pressure was 136 Mm. and the urine of this period contained 5.3 Gm. of sugar. The rate of injection was then increased to 0.0015 mg. per Kg. per minute and at the forty-eighth hour the systolic pressure was 154 Mm. The injection was then stopped momentarily and the pressure fell to 130 Mm. and rose promptly to 157 Mm., when the injection was again resumed. The urine during this period contained no sugar. During all of this time the animal seemed very thirsty but refused food and vomited repeatedly. Later the abdomen became distended and death occurred on the fourth day of the injection. Autopsy disclosed a marked dilatation of the stomach and intestines and pulmonary edema, which was probably the cause of death.

Animal No. 4.—Female. Wt. 10.4 Kg. Control measurements of the systolic blood pressure were as follows: 4-24-35, 108 Mm.; and 4-26-35, 108 Mm. The urine was sugar-free. The intravenous injection of epinephrine at the rate of 0.001 mg. per Kg. per minute was started on 4-27-35. On 4-29-35 the rate of injection was increased to 0.002 mg. per Kg. per minute and the blood pressure taken at this time was 110 Mm. At the 72nd hour of injection the pressure was 118 and at the 96th hour 122 Mm. The blood sugar at this time was 118 mg. The rate of injection was then increased to 0.0025 mg. per Kg. per minute. At the 120th hour the pressure was 104 Mm. When the injection was stopped it fell to 70 and rose to 132 Mm. when the injection was resumed. The blood sugar at this time was 107 mg. At the 144th hour the blood pressure was 122 Mm., fell to 66 Mm. when the injection was stopped, and rose to 126 Mm. when the injection was resumed. The blood sugar at this time was 86 mg. The rate of injection was then further increased to 0.003 mg. per Kg. per minute. On the 216th hour the pressure was 105 Mm. At the 240th hour the injection was stopped accidentally for seven hours and at the end of this time the presure was 88 Mm. When the injection was resumed the pressure rose to 111 Mm. On 5-8-35, 264 hours after the beginning of the epinephrine injection, the blood pressure was 136 Mm., fell to 92 Mm. when the injection was stopped, and then rose to 127 Mm. when the injection was resumed. The blood sugar at this time was 57 mg. Shortly after the beginning of the injection the animal became depressed and vomited frequently. After the third day it refused all food but continued to drink water. On the sixth day water was refused and the animal became progressively weaker and lethargic. Death occurred on the twelfth day and autopsy revealed bronchopneumonia, fatty infiltration of the liver, and apparent atrophy of the adrenal glands (each weighed 0.6 Gm.).

Animal No. 5.—Male. Wt. 11.1 Kg. Control measurements of the systolic blood pressure were made as follows: 5-27-35, 144 Mm.; 5-28-35, 142 Mm.; and 5-29-35, 142 Mm. The blood sugar was 84 mg. and the urine was sugar-free. On 5-31-35 the intravenous injection of epinephrine at the rate of 0.002 mg. per Kg. per minute was started and during the first 24 hours 4.2 Gm. of sugar was excreted in the urine. At the end of 24 hours the blood sugar was 76 mg. and the systolic blood pressure measured 170 Mm. Hg. When the injection was stopped momentarily the pressure fell rapidly to 120 Mm. All subsequent specimens of urine were sugar-free. At the 72nd hour the blood sugar was 85 mg., the pressure was 160 Mm. and it dropped to 104 Mm. when the injection was stopped. At 120th hour the blood sugar was 82 mg. The pressure measurement was unsatisfactory but when the injection was stopped the pressure measured 98 Mm. and rose to 177 Mm. when the injection was resumed. At the 240th hour the blood sugar was 65 mg. and the blood pressure 143 Mm. When the injection was stopped it fell to 110 and then rose promptly to 178 Mm. when the injection was resumed. At the 288th hour the blood sugar was 53 mg. and the blood pressure only 113 Mm. However, when the injection was stopped it fell to 80 Mm. and rose to 123 Mm. when

the injection was resumed. At the 336th hour the pressure was 120 Mm., it fell to 97 Mm. with the injection off, and rose to 119 Mm. with the injection reestablished. Throughout the entire period of injection the animal displayed marked anorexia, panting, frequent vomiting, progressive weakness and apathy. On the fifteenth day of injection it was found dead and no gross changes were discovered at autopsy.

Similar experiments were undertaken upon six additional animals and the results were found to corroborate those listed in the above protocols in all essential respects. The details will, therefore, be omitted. In order to obtain additional information with respect to the behavior of the blood sugar during the continuous intravenous injection of epinephrine in the

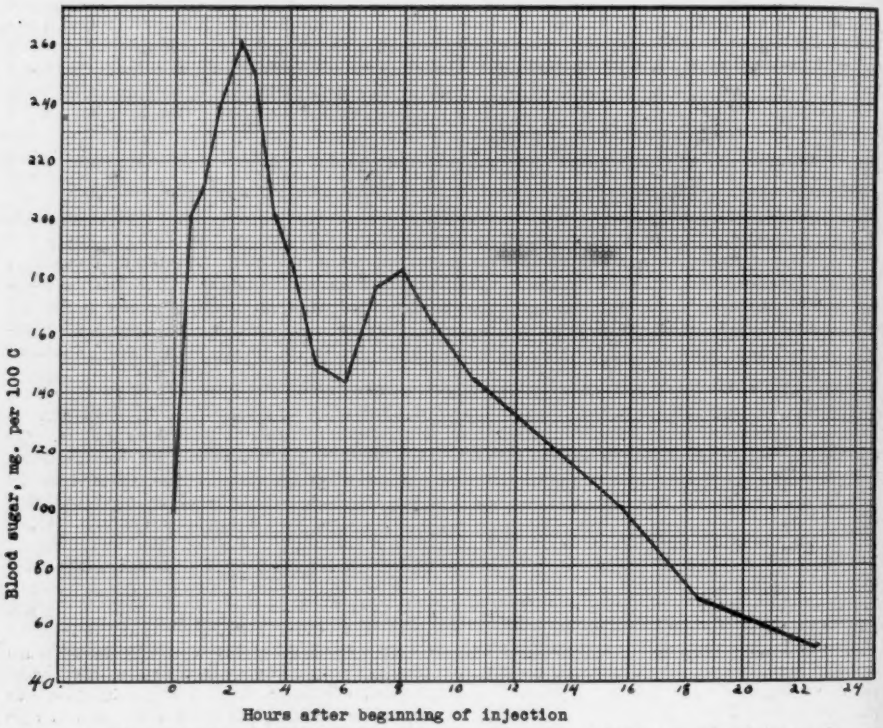

CHART 1.—Curve showing the effect of the continuous intravenous injection of epinephrine at the rate of 0.0015 mg. per Kg. of body weight per minute on the level of the blood sugar.

unanesthetized dog, experiments were performed on five animals employing the same method, except that measurements of the blood pressure were not made. The animals were fasted for several days and no food or water was given during the experiment. The results of a typical experiment are illustrated in the curve in Chart 1. In three of the animals epinephrine was given at the rate of 0.0015 mg. per Kg. of body weight per minute and in the remaining two at the rate of 0.002 mg. In every case the blood sugar rose to a peak within the first hour and thereafter gradually declined, reaching normal values usually within the first 18 hours. At the end of 24 hours the blood sugar was commonly found to be definitely below normal in some

CHART 4.—Tracing showing the hypertension produced by the continuous intravenous injection of epinephrine at the rate of 0.002 mg. per Kg. per minute for 28 hours. Note the fall in pressure when the injection was stopped and the high rise when the injection was again resumed.

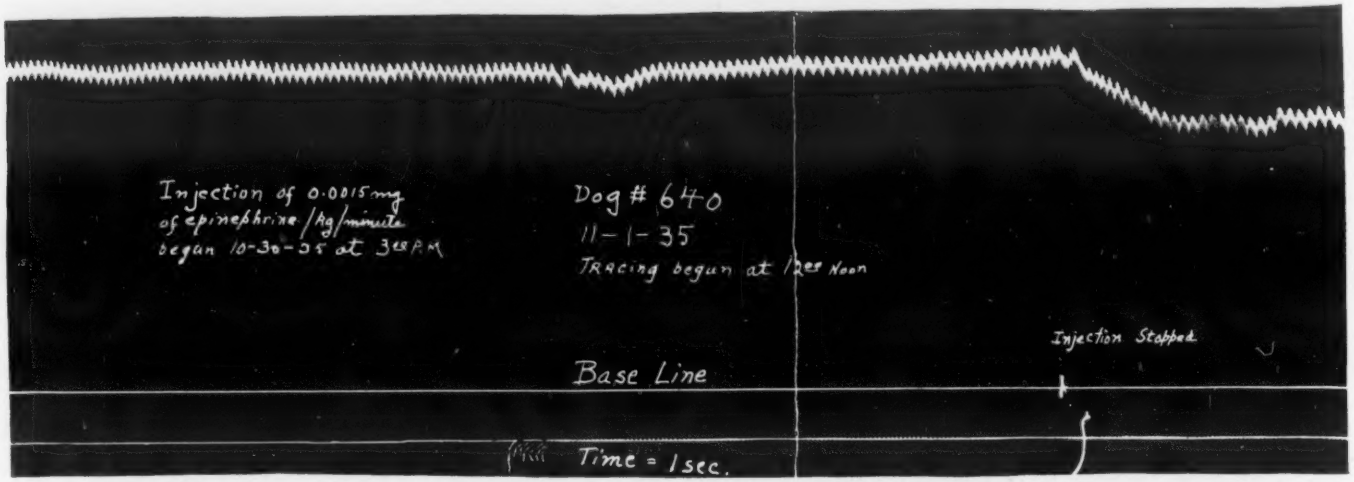

CHART 2.—Tracing showing hypertension produced by the continuous intravenous injection of epinephrine at the rate of 0.0015 mg. per Kg. per minute for 45 hours. Note the fall in blood pressure when the injection was stopped.

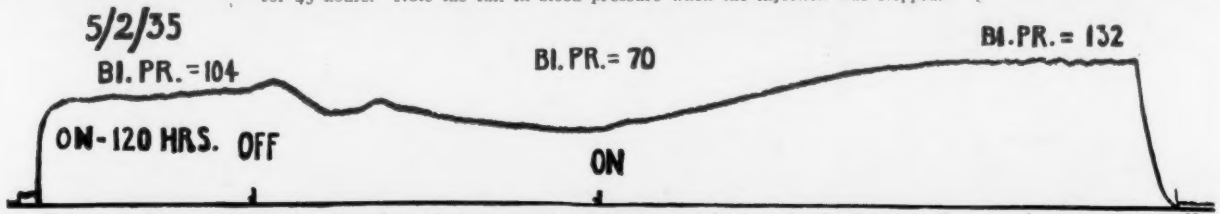

CHART 3.—Diagram illustrating the effect of the continuous intravenous injection of epinephrine at the rate of 0.0025 mg. per Kg. per minute on the mean systolic blood pressure. Note the fall in pressure when the injection was stopped and the high rise when the injection was resumed at the same rate as before.

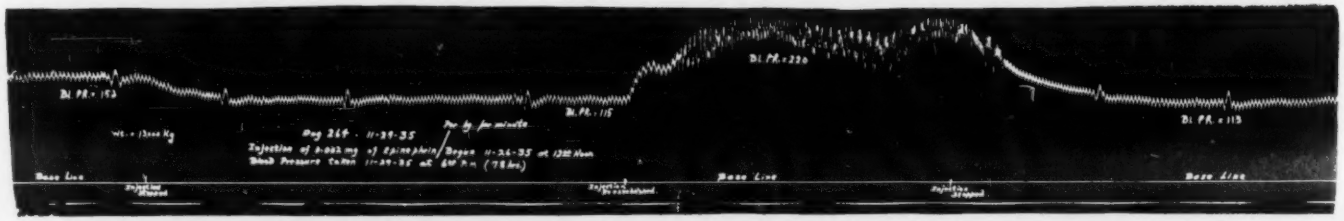

CHART 4.—Tracing showing the hypertension produced by the continuous intravenous injection of epinephrine at the rate of 0.002 mg. per Kg. per minute for 78 hours. Note the fall in pressure when the injection was stopped and the high rise when the injection was again resumed.

cases approaching the shock level. Varying amounts of sugar were found in the urine during the first 24 hours but none in subsequent samples.

Discussion.—The data secured are consistent and prove that it is possible to maintain a varying degree of hypertension in normal dogs for periods up to two weeks by the continuous intravenous injection of epinephrine. The amount required was found to be from four to ten times the minimum dose that C. A. Dragstedt found would produce a temporary pressor response and also correspondingly larger than the amount that Stewart and Rogoff estimated as the normal output of the adrenal medulla. A compensatory adjustment of the cardiovascular system to the hemodynamic effect of the epinephrine was observed in every case. After the initial high rise the pressure decreased very materially although it still remained above the control level (Charts 2, 3, and 4). The nature of this compensatory reaction has not been determined. The prompt fall in blood pressure, sometimes to very low levels, when the injection was temporarily stopped is also of great interest, particularly in view of the clinical observations that removal of a chromaffin tumor in patients with paroxysmal hypertension has sometimes been followed by a similar and often alarming fall in blood pressure (Porter and Porter,[29] Shipley,[34] and Coller, Field, and Durant).[25] Does this mean that the continuous injection of epinephrine in the one case and the hypersecretion of epinephrine in the other have caused a functional depression of epinephrine secretion by the normal chromaffin tissue and this is manifested by the fall in blood pressure when the extraneous epinephrine is excluded? An analogous situation is found in other endocrine organs, notably the parathyroids, where the removal of an hyperfunctioning adenoma may produce temporary acute parathyroid deficiency even though a normal amount of parathyroid tissue remains. If this should be true the finding is definite evidence in support of the tonus theory.

While it is true that a definite hypertension may be maintained up to two weeks by experimental hyperadrenalemia, the other systemic effects of the epinephrine are so severe that the animal cannot survive for a much longer period. It is probable that an almost complete inhibition of gastrointestinal motility occurs at the outset of the injection and persists until the animal dies. There is also evidence of a profound derangement in carbohydrate metabolism and this may contribute to the fatal issue. That the deleterious effects are due to the epinephrine is indicated by the fact that animals injected in the same manner with physiologic salt solution tolerate the procedure for many weeks with no adverse symptoms. It is apparent then that the data obtained in this investigation offer no support to the view that any form of persistent hypertension in man could be due to an hypersecretion of epinephrine. On the other hand, it seems very probable that a degree of hyperadrenalemia sufficient to produce hypertension would soon cause the death of the individual from the other systemic effects of the hormone.

SUMMARY

A sustained hypertension was produced in normal dogs for periods up to two weeks by the continuous intravenous injection of epinephrine. The amount required, however, was sufficient to cause death from the other systemic effects of the hormone of which the inhibition of motility of the gastro-intestinal tract and the derangement in carbohydrate metabolism were probably the most important. For this reason it does not seem probable that persistent hypertension in man will be found to be due to hyperadrenalemia.

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POSTOPERATIVE THROMBOSIS AND EMBOLISM

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NEW YORK

THERE is no greater tragedy in surgery than to have a patient who is apparently convalescing normally, either die in his sleep about the tenth day postoperative, or just as he is preparing to go home, suddenly have an attack of shortness of breath and expire.

For many years studies have been made on the frequency of these complications in various series of operations but no real attempt was made to see if there was some underlying factor that made some patients more susceptible to this condition than were others.

These studies were started in 1928 by Bancroft and Stanley-Brown, and continued until 1934, when Doctor Quick was associated in the work for two years. Since 1936 the work has been carried on at the Presbyterian Hospital and Columbia University, through a grant by the Carnegie Corporation of New York, and Doctor Chargaff has been directing the biochemical studies. The clinical work, since 1936, has been carried on at the Presbyterian Hospital and also, through the kindness of Doctor Heuer, at the New York Hospital.

The results of the studies, from 1928 to 1932 and from 1932 to 1934, have been the basis of two publications[1, 2]; therefore, the statistics presented in those reports will not be mentioned in this presentation. It will be necessary, however, to briefly review the reasons for initiating the study, and certain alterations in technic that have occurred.

We are confident that the physical factors accepted by most authors; namely, dehydration, stasis, infection and trauma, are the main causes of postoperative thrombosis, thrombophlebitis and embolism. In addition to these factors, it is felt that there must be a biochemical change in the blood which precedes and accompanies thrombophlebitis and embolism, because all of the physical factors may be present in certain patients and no accident occur, while in other patients the minimum number of the physical factors may be present and an accident result. We believe also that everywhere in medicine if there is an *hyperactivity*, there is also an *hypoactivity*: for instance, one may find *hyperacidity* and *hypoacidity*, *hyperthyroidism* and *hypothyroidism*. It is recognized that there are definite bleeding diatheses, such as can be found in hemophilia, certain purpuras and obstructive jaundice. If, therefore, it is true that there are potential bleeders, one can readily assume that there are potential clotters. If this theory be true, it seemed to us that a careful analysis of the blood factors involved in clotting would reveal a significant change before a thrombus occurs. From the numerous

and complicated theories of blood coagulation we took the most simple ones, in the hope of being able to estimate these factors by quantitative tests. the theory we accepted was as follows: Prothrombin + calcium + thrombokinase created thrombin. Thrombin, when combined with fibrinogen, gives fibrin, or clotted blood.

The above named factors are the main activators of blood clotting, and it may be said that the only inhibitor of blood clotting which so far has been isolated from the human body in a reasonably pure state is heparin. It cannot be said yet whether antithrombin and heparin are the same substance. In our original studies we considered antithrombin as part of our clotting index, but after Quick[3] had studied the subject, he felt that a test for such a substance was not entirely accurate and complicated the technic.

Heparin, a chemical substance which occurs in almost all mammalian organs and which is capable of preventing the clotting of blood both in vitro and in vivo, is probably the most active postoperative anticoagulant. Heparin was originally discovered in the liver by Howell and Holt. It is considered as a mucoitin polysulfuric acid. We have felt since the beginning of our work that if we approached the solution by an analysis or study of heparin, we would go far toward solving the problem of thrombosis. One of us, Chargaff, has developed a simple method of estimating the potency of heparin. The inhibitor unit is defined as the smallest amount of inhibitor which will raise the blood clotting time of 0.1 cc. of chicken plasma to four times its normal value under carefully controlled experimental conditions. So far this test has been utilized solely in defining the potency of preparations of heparin produced by manufacturing chemists. We hope to see whether this test is of any value in studying the clotting or bleeding tendencies of patients. In studying heparin it was found that there are several synthetic substances which act as anticoagulants. Notable among these is a polysaccharide acid occurring in certain red algae. We have not yet been able to test whether these substances have any clinical significance.

Before describing the tests for blood clotting factors and giving the result of our prophylactic therapeutic program, it might be wise to describe the factors entering into blood clotting, *viz.*: fibrinogen, calcium, prothrombin and thromboplastin.

Fibrinogen.—It is normally present in blood plasma to the extent of 0.3 to 0.75 Gm. per 100 cc. of blood. In infections it is apt to be high, whereas in certain profound liver disturbances, low concentrations have been found. In our analyses of patients who have suffered from vascular clotting we have felt that a fibrinogen of over 0.8 Gm. per 100 cc. of blood is significant of a tendency toward phlebitis associated with a definite infection.

Calcium.—The indispensability of calcium in the clotting process has led to the belief that in certain hemorrhagic diseases, a deficiency of this element in the blood may be present. At the onset it must be emphasized

that even in the most marked hypocalcemia of parathyroprivia, no definite alteration of blood clotting can be demonstrated, and likewise the high blood calcium in hyperparathyroidism does not bring about any marked change in the coagulation time, and even in cases in which the blood calcium is 100 per cent above normal, no intravascular clotting has been reported. Clinically normal blood calcium is found in hemophilia and in the hemorrhagic diathesis of obstructive jaundice. No elevation of blood calcium has been demonstrated in spontaneous thrombosis.

Prothrombin.—Although a few investigators have doubted or even denied the actual existence of such a substance as prothrombin, there is overwhelming evidence that there exists in blood an agent which is the precursor of thrombin. It has the properties of a proenzyme, and therefore its isolation in pure form at present offers insurmountable difficulties. Its determination must therefore depend on first converting it to thrombin, which can be determined from the clotting time. The thrombin is associated with the globulin fraction of the blood and appears to be limited to the serum. It varies to a marked degree in both bleeding and clotting diseases.

Thromboplastin.—Much confusion concerning this substance still exists and it is still called by a variety of names such as tissue extract, tissue juice, tissue fibrinogen, cytozyme, cephalin, etc. The substance appears to be a proteinphospholipoid which possesses the power to convert, in the presence of calcium, prothrombin into thrombin. Unlike prothrombin, which appears to be limited to blood plasma, thromboplastin is widely distributed in the body. In circulating blood it is locked up in the platelets, but in shed blood it is liberated when the platelets disintegrate. The exact reason for the platelet lysis is not known.

During the past year, one of us, Chargaff, has spent considerable time in studying the activators of blood clotting contained in platelets. An activating lipoid was isolated from 800 milligrams of almost pure thrombocytes. It was shown to be associated with a cephalin fraction. Thus for the first time the importance of the blood platelets in the clotting process could be demonstrated by chemical means. It was also shown that platelets contain an anticoagulant. This finding seems to be of importance for a theoretic understanding of the occurrence of certain blood diseases. If, in certain pathologic cases, the permeability of the blood cells for the activator or the inhibitor of clotting were disturbed, or if one or the other of these agents were entirely absent, the development of an increased bleeding or clotting tendency might be readily understood. We hope to continue this study.

Since 1934 we have examined patients routinely preoperatively and five and nine days postoperatively. It is obvious that we cannot tell preoperatively what patients are apt to have an accident, and the five and nine days postoperative are, in general, the danger periods. We rely on the tests for prothrombin and fibrinogen. The prothrombin test, which was definitely

simplified by Quick, is a simple one and can be performed in any laboratory. The fibrinogen test is somewhat more complicated but is of distinct value. We had hoped we could finally simplify the analysis so that only one test need be utilized which would give a true index of the patient's bleeding and clotting tendencies. This, however, has not been possible. The prothrombin test, designated by us as the plasma clotting index, is more indicative of clotting tendencies wherein infection is at a minimum, while the fibrinogen test, when high, suggests infection and the likelihood of thrombophlebitis.

TEST FOR PLASMA CLOTTING INDEX

(1) Put 1 cc. of M/10 sodium oxalate in test tube and add 9 cc. of blood. Let it stand until red cells settle out (not longer than one hour).

(2) Put 0.1 cc. of plasma in each of two tubes. To tube No. 1 add 0.1 cc. M/40 calcium chloride. To tube No. 2 add 0.2 cc. M/40 calcium chloride. Shake and put in water bath heated to 37° C. Time exactly and record shortest time required for the formation of a solid clot. Normal clotting time varies from one minute to one minute 45 seconds.

To Make M/10 Sodium Oxalate.—Dissolve 13.4 Gm. sodium oxalate in one liter of distilled water.

To Make M/40 Calcium Chloride.—Prepare a stock M/10 solution by dissolving 11.1 Gm. of anhydrous calcium chloride in one liter of water. Then take 25 cc. of stock solution and dilute to 100 cc.

Index.—The normal clotting time with this solution is one minute 45 seconds or 105 seconds, and this is used as the numerator, and the patient's clotting time in seconds is used as the denominator; the plasma clotting index is determined. The normal range of this index is between 0.8 and 1.05: below 0.8 there is a tendency to bleed, while above 1.05 there is a clotting tendency.

Technic.—Blood must be drawn quickly with a minimum of tissue trauma, as a small amount of tissue juice in the specimen will spoil the test. The blood must be mixed quickly and thoroughly with the oxalate, as the calcium must be removed immediately; otherwise thrombin forms and remains in the plasma and shortens the clotting time when the plasma is recalcified.

TEST FOR FIBRINOGEN

(1) Mix 1 cc. of plasma with 25 cc. of 0.9 per cent sodium chloride solution. Add 2 cc. of 0.25 per cent calcium chloride. Remove clot by wrapping it around a small stirring rod. Allow it to stand for one hour. Remove stirring rod covered with fibrin.

(2) Place stirring rod in a small tube, add 0.5 cc. of 10 per cent sodium hydroxide and place in boiling water for 30 minutes. Cool, and add 7.5 cc. of distilled water.

(3) Standard. Two cubic centimeters of standard tyrosin (containing

250 mg. per 100 cc. of N/10 hydrochloric acid) are mixed with 5.5 cc. of distilled water and 0.5 cc. 10 per cent sodium hydroxide.

(4) To unknown and to standard add 1 cc. of phenol reagent (Folin and Ciocalteu[6]) and 3 cc. of 20 per cent sodium hydroxide. Mix and read in colorimeter after 30 minutes.

(5) Calculation. 10/R x 100 x 0.5 mg.x13; mg. fibrin in 100 cc. of plasm.

This procedure is a modification of the method of Andersch and Gibson.[7]

Range of fibrin: 350 to 750 mg. per 100 cc.

The study of any particular surgical therapeutic program is apt to make all members of the staff tissue conscious. The adoption of the silk technic has tended to make surgeons conscious of the necessity of delicate handling of the tissues. The study of a prophylactic regimen against thrombosis and embolism makes one conscious of certain postoperative therapeutic measures which we wish to mention very briefly:

(1) In abdominal cases every effort should be made to reduce the postoperative nausea and vomiting in order to keep the abdominal wall and field of operation quiet. The Levin tube, inserted through the nostril when the patient is conscious, is routinely introduced wherever vomiting occurs to any degree.

(2) Early exercise of the extremities is advised in order to prevent venous stasis.

(3) In our opinion, tight abdominal dressings should be eliminated. With the advent of the Gatch bed, often with the patient in a semi-erect position, tight abdominal dressings followed by moderate distention tend to compress the femoral vein as it passes beneath Poupart's ligament. Therefore we believe that sufficient dressings should be applied while the patient is on the operating table to cover the incision and should be lightly strapped with adhesive. On the first day postoperative any dressings that are tight should be loosened. As distention is a factor in increasing abdominal pressure, and therefore venous stasis, we believe that food should be given early. Alvarez and others have shown that when a bolus of food passes through the pylorus, intestinal peristalsis is stimulated, which will carry with it gas as well as solid material, thereby tending to prevent fermentation.

(4) Dehydration. Even in uncomplicated cases the excess of fluid loss from the body over the fluid intake in the first 48 hours postoperative is tremendous. If vomiting persists and the temperature is high, dehydration occurs very rapidly. We strongly advise intravenous administration of fluid immediately postoperative and continued until the patient is taking an adequate amount by mouth.

If the examination of the blood taken either pre- or postoperatively shows a high plasma clotting index and a high fibrinogen content, the patients are placed on a carbohydrate and fluid diet, limiting their fats and proteins. We have shown, both in dogs and humans, that this diet, which for the sake of convenience we have called a bleeding diet, will diminish the bleeding factors, while a diet rich in nucleoproteins and fats will cause

a marked increase. In addition we advise the administration of sodium thiosulphate. We give 10 cc. of a 10 per cent solution of sodium thiosulphate intravenously for three successive days, repeating the series after an interval of one day, if the bleeding factors still remain high. We have seen no ill effects from its administration when given at an interval of five days after the operation. There have been two cases reported where it has been given immediately postoperative in which emboli occurred, and this may be due to the fact that operative clots were liberated before organization had occurred. Sodium thiosulphate may theoretically liberate sulphur. It may eventually form the basis for the synthesis of other sulphur-containing substances, for example, glutathione or even heparin. Glutathione is a peptide which plays an important rôle in the oxidations occurring in the animal body. It also has been suggested that it may be of importance in blood clotting.

In our early studies at the Fifth Avenue Hospital, over 8,000 operative cases were analyzed and the results have been published. We found at that time that patients might be readily divided into three classes, *viz*: those with a tendency to bleed; those with normal clotting tendencies; and those with a tendency to clot. In our early studies we observed that all cases in which vascular accidents of a thrombotic nature occurred had blood with high clotting factors, but in that series, with our old clotting index, there were about 34 per cent of postoperative cases who had high indices. Only a very small percentage of these developed vascular accidents. There were, however, many of this group who did not develop any accident whose postoperative course was not normal in that they ran a higher postoperative temperature for a longer period of time than the average and even left the hospital with a slight elevation of temperature. One might assume that some of these patients had a deep thrombosis or thrombophlebitis which was not evident in the vessels of the extremities and in whom no serious accident occurred.

With the new tests the postoperative highs now consist of from 12 to 14 per cent of all postoperative cases and with three exceptions, which will be enumerated later, the accidents have occurred in this group.

During the past two years we have been carrying on our tests at the Presbyterian Hospital and at the New York Hospital. At each hospital one service has been assigned for our tests and prophylactic treatment and the other has been used as a control.

At the beginning of our work at the Presbyterian Hospital our association was not very close with the active postoperative cases and hence the prophylactic treatment was not always carried out. At the present time this relationship is much closer, because Doctor Olson, a Senior Research Fellow, has been assigned to this particular program.

The blood of 920 cases was examined. Of these, 111, or 12 per cent, showed high clotting indices. Only 46 per cent of these highs received prophylactic treatment. In the treated case group no accident occurred:

In the untreated group nine accidents occurred. Two of these were unrecognized, as the fibrinogen was the only high factor. Another case was an old lady of 73, with myocarditis, who had a cholecystectomy performed. Both postoperative tests, on the fifth and ninth days, were normal. On her nineteenth day she developed signs of a pulmonary infarction but there was no demonstrable phlebitis. On the control division there were 12 accidents.

At the New York Hospital, under Doctor Heuer and Doctor Andrus, the analysis may be divided into two periods. During the first six months, until March, 1936, 333 cases were examined. Of these, 48, or 14 per cent, had high clotting indices, but only 28, or 8 per cent, were treated with sodium thiosulphate. No deaths occurred in the treated group which can be attributed to thrombosis. One postoperative accident occurred, however, which is described in the appended case report.

Case Report.—A Negro woman, age 52, was admitted June 25, 1936, for ligation of the saphenous vein and injections. Preoperatively her plasma clotting index was 1.0, her fibrinogen 0.34, platelets 170,000 and lysis 11 per cent. Three days postoperatively she developed a temperature of 102° F. and complained of pains in her chest. On the following day her plasma clotting was 1.15, fibrinogen 0.91 per cent, platelets 180,000 and lysis 27 per cent. She was treated with sodium thiosulphate. Roentgenologic examination revealed a pulmonary infarct. Nine days postoperatively her clotting index was 1.05, fibrinogen 0.82, platelets 220,000 and lysis 22 per cent. Temperature and pulse subsided and she was discharged on the fifteenth postoperative day. On the control floor during the same period there occurred five instances of emboli, one of which was fatal, and one case of phlebitis.

Since March the work has been continued, but in the control group the intern staff has run plasma clotting tests only. 242 cases were observed on the treated service, and 30 showed high indices. Only 70 per cent of the highs received treatment. One unexplained accident occurred in the group. A patient with a carcinoma of the cecum and intraperitoneal abscess tested high on the fourth day, was treated, was normal on the ninth day, and developed a nonfatal pulmonary infarction on the fourteenth day. In the untreated group there were one pulmonary embolism and one pulmonary infarction on the third postoperative day. The latter recovered rapidly under administration of sodium thiosulphate. On the control service, where only plasma clotting tests were made, two pulmonary emboli occurred. One of them had a normal plasma clotting test, but no fibrinogen estimation was made.

During the past two years we have been much interested in the work that has been done by Hedenius and Willander[4] in Stockholm, by Lenggenhager in Berne, and Best[5] in Toronto, in the utilization of heparin as a postoperative prophylactic agent. Lenggenhager offers the theory that heparin neutralizes the thrombin arising from the wound, and injects heparin in small doses at the time of operation into the muscles surrounding the incision. He believes that heparin combines with thrombin at the very place of absorption and neutralizes it. He states that in this manner smaller

quantities of heparin can be used than if it were injected far from the site of operation. He believes, therefore, that the whole operative site of the wound should be saturated with heparin and he advises its injection into the muscles and not into the subcutaneous fat.

Newer preparations of heparin are much more stable than those previously presented by manufacturing chemists.* In our early studies we found that heparin injected intravenously lowered the clotting factors in the blood for only an hour or two and then the blood regained its normal tendency. In this present method of injecting into the muscles about the operative site, the heparin is absorbed much more slowly and therefore must have a longer period of potency. The question has been raised that the injection of heparin may cause hemorrhage in or near the operative site, and in one of our animals, where no adrenalin was used, this proved to be the case. It is for this reason that adrenalin is added to the mixture. We have not had sufficient experience as yet to state our conclusions, but hope in a later communication to give these data. There are, however, certain objections to the routine use of an anticoagulant. Only a small percentage of patients, 1 or 2 per cent, of all postoperative cases develop thrombosis and embolism, and it seems a rather expensive procedure to utilize this drug in all cases in order that it may benefit 1 per cent. We believe that the clotting factors, as we have described them, are a fairly accurate index of a patient's clotting tendencies and that if these cases are observed early and placed on a bleeding diet and given sodium thiosulphate, the morbidity may be definitely reduced.

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DISCUSSION.—DR. J. SHELTON HORSLEY (Richmond, Va.): I wish to speak about the incidence of pulmonary embolus or thrombus following the continuous intravenous administration of fluids. There seems to be a growing prejudice against this very valuable therapeutic measure because of the supposed high incidence of pulmonary embolism following it. The measure is so valuable that there should be very real grounds for discrediting it. Coller and his associates have called attention to the vital need of fluids after any extensive operation, and when the patient is dehydrated and comes

* We are indebted to Messrs. Hoffman-La Roche, Inc., Basel, for a supply of a very satisfactory preparation of heparin.

to operation, the intravenous administration of fluids is extremely important. Giving the gastro-intestinal tract physiologic rest after operations upon the stomach or intestine, and particularly in appendicitis or in spreading peritonitis, cannot be well carried out without the intravenous administration of fluids. Proctoclysis violates the well known principle of resting tissues that are inflamed, and imposes a burden of increased physiologic activity on the colon.

In a very well known clinic recently it has been reported that in a series of 50 cases in which intravenous dextrose and saline were given, there were three instances in which there was pulmonary embolism and in one of which there was a pulmonary infarction, and three of these patients died. Such an astounding mortality rate is, of course, extremely serious.

About two years ago I reviewed, for the preceding five years, the number of patients in St. Elizabeth's Hospital, Richmond, Va., in whom the intravenous administration of fluids had been given for a period of three hours to four days. Not infrequently after a partial gastrectomy and in peritonitis cases, it is used continuously for three days. I have recently gone over our statistics since that time, that is, from April 1, 1935, to June 1, 1937, making a period of seven years and two months in the total review. St. Elizabeth's is a private hospital with a medical and surgical service, but the largest proportion of the patients are surgical. During this period of seven years and two months there have been 8,925 admissions to the hospital, and in about 3,170 patient fluids have been given intravenously for a period of three hours to several days. In a great majority of these cases the fluid given was 5 per cent dextrose in Ringer's solution. In some it was 5 per cent dextrose alone, and occasionally 10 per cent dextrose was given for a short time followed by 5 per cent dextrose in Ringer's solution. As a rule, however, we use the isotonic 5 per cent dextrose solution, unless there is edema of the lungs or a decreased kidney secretion.

We give continuous intravenous solutions in about one-fourth of all patients admitted to St. Elizabeth's Hospital. We use the term "continuous" for anything requiring three hours or more of administration. During this period of seven years and two months there have been six deaths from pulmonary embolism, all following operation, a percentage rate of 3.57 of all of the surgical deaths. This rate is less than usually obtained in large institutions. Thus the Reichenberg Clinic[1] reports 16.6 per cent fatalities from pulmonary embolism.

Of the six deaths, one of the patients had had no intravenous injection of any kind. In another case, when the patient was obviously dying from postoperative pneumonia, 20 cc. of 50 per cent dextrose solution were given a few hours before death. Necropsy showed thrombosis of a pulmonary vessel in the pneumonic area. In a third case, following a suprapubic prostatectomy the patient was given intravenously 1,600 cc. of 5 per cent dextrose in Ringer's solution, and the following day he was given 1,000 cc. of the same solution. Seventy-nine days after the last intravenous injection he died suddenly, apparently of pulmonary embolism, though necropsy was not permitted. In the fourth case the patient received 1,000 cc. of 5 per cent dextrose in Ringer's solution the first day after an operation for a gangrenous appendix, and suddenly died 17 days later while sitting in a chair and about to leave for home. The fifth patient received 500 cc. of 5 per cent dextrose in Ringer's solution the day after operation for a suprapubic cystotomy, and died suddenly of pulmonary embolism 18 days later. The sixth patient received 8,000 cc. of dextrose in Ringer's solution intra-

venously over a period of three days after a gastro-enterostomy, and died of pulmonary embolism 16 days after the operation.

I am confident that in many cases the continuous intravenous administration of dextrose in Ringer's solution has been life saving. Aside from this, too, when it seems probable that an operation will be severe or prolonged, a cannula is inserted and intravenous dextrose in Ringer's is begun when the operation is begun. In this way such operations as abdominoperineal excision of the rectum, for instance, can usually be carried out in one stage and shock can be avoided or mitigated by increasing the flow of the solution. Donors are provided for transfusion at the end of the operation if the blood pressure tends to fall in spite of the intravenous solution.

We now use a graduated glass ampoule containing 1,000 cc. of the fluid to be administered. This ampoule is entirely of glass, has no stopper, and is prepared by the Sterisol Company. We have had no reactions in the past three years, and before that time there were only three comparatively slight reactions, all in septic cases with chills, before the solution was given.

It seems to me that one of the chief causes of pulmonary embolism, as reported elsewhere, is the use of the drip apparatus. Why this should be adopted it is difficult to understand. The only advantage claimed for it is that the flow can be regulated, but in the large, graduated ampoules or in the narrow buret that is graduated the flow can be regulated by placing a small strip of adhesive plaster at the level of the fluid and another farther down, indicating the amount to be given in an hour. In fact, the rate of the drops is so often irregular due to the back pressure from the vein that this method of regulating the flow by observation on the ampoule or buret is, I believe, more accurate than counting the drops, and it can be observed at a glance instead of having to count the drops.

The more serious feature is that this drip apparatus acts as a glorified air bubble within the tube. When the patient strains or vomits, the back pressure in the vein will retard or prevent the flow of the solution. This will slow down the drip, or almost stop it. When the patient stops straining, and the rate of venous flow is more rapid, small bubbles of air are sucked over into the vein. They are doubtless not sufficient to cause serious complication so far as the heart is concerned, but they are carried into the pulmonary artery and may cause a thrombus later on.

The regulation of the heat at which the fluid is applied is unnecessary. It is important not to have the fluid too hot, but ordinary room temperature is all that is necessary. The heat that can be carried over by 100 to 150 cc. of fluid an hour is almost negligible, and can be very easily supplied by hot applications to the body.

Making the apparatus simple like this not only adds to its efficiency but should increase its application; giving isotonic dextrose is also an obvious advantage as it does not tend to irritate the vein and cause a local thrombus. I am confident that if the dextrose is pure and if the solutions are properly prepared, this simple method of administration, discarding the complicated apparatus for keeping the fluid warm and the dangerous drip apparatus, will add materially to this valuable method of treatment.

REFERENCE

[1] Schmid, H. H.: Zentralblatt für Gynakologie **61**, 307–317, 1937.

DR. JOHN HOMANS (Boston): Doctor Bancroft and his associates are the first, so far as I know, who have studied postoperative thrombosis and embolism from the standpoint of blood chemistry at the bedside. They have

devoted themselves to the problem of coagulation, or clotting, preferring to ignore the almost more troublesome question as to why platelets sometimes stick to the blood vessel walls, the process generally known as thrombosis.

To say that they ignore the problem of thrombosis is perhaps unfair, for not only does their system of corrective treatment include an effort to change the chemistry of the blood, but they make a decided point of hastening the current of blood from the legs toward the body, the region where most postoperative thrombosis occurs and from which most embolism comes. For it is in the slowed current that thrombosis most often begins. Thus, Bancroft and his coworkers are not performing an experiment as well controlled as seems to me desirable, and I should like to suggest a somewhat different method of attack.

It seems to me true that fatal embolism often arises from a spot which pathologists never discover, and that outspoken phlegmasia alba dolens, that is, the femoro-iliac thrombophlebitis, is on the whole a rather infrequent source of embolism. Aschoff even maintains that a fatal embolism can arise only from the lower femoral, a statement with which most will disagree. But what he means is that a long, free waving, propagating thrombus, long enough and large enough to cause death if detached, can most readily form in the popliteal region. However this may be, I would ask you to believe that there are several clinical forms of thrombophlebitis, and that an enforced life in bed, apart from the undoubted influence of trauma, operative or otherwise, does something to the return flow of blood from the lower limbs. This must be something more than the slowing of the current. It may be related to the remarkable acute inflammation about the iliac vessels which I have observed once or twice in pelvic explorations of phlegmasia alba dolens, or perhaps it is concerned with some product of muscle atrophy, that is, the rapid atrophy which so quickly sets in upon life in bed, particularly in the legs.

Thrombosis in the great venous plexuses of the calf of the leg has often been proved to be the source of a fatal embolism. It very readily sets up a long, free propagating clot, and would more often be found if its presence were suspected. Clinically, it is almost undetectable. The question is whether Doctor Bancroft's "thrombophilic" background is essential to such processes and to the dangerous propagating types of thrombosis to which I have just alluded. My own feeling is that the blood chemistry, except for dehydration, is not a prime factor. Therefore, I am inclined to concentrate upon the influence such as distention and the correction of vomiting as suggested by Doctor Bancroft, and upon exercise and actual elevation of the legs. Sitting up in bed for any great length of time is undesirable, but how long patients can remain with their heads lower than their feet without subjecting themselves to some other complication, I do not know. In any case, elevation to hurry the return flow of blood is so strikingly beneficial in limiting and healing visible superficial thrombosis that one can hardly believe it is not equally effective in preventing as well as limiting the invisible deep thrombosis.

Doctor Bancroft may well be right in concentrating upon the chemistry of the blood in general, but I could wish that he would devote his ingenuity and patience to the blood flow from the legs and to the rather mechanical side of the subject of which I have spoken. I do not doubt that he is only at the beginning of his discoveries.

DR. HOWARD LILIENTHAL (New York): Alton Ochsner wrote an interesting paper on the action of hirudin, as furnished by leeches, in cases

of thrombosis of the veins. I have tried it in several cases and have found that it acted like magic, that the thrombophlebitis disappeared within 48 hours. That does not mean that the hirudin as applied by the leeches has to be put near the vessel. Anywhere in the general neighborhood will do. I intend to apply four leeches in my abdominal cases, somewhere between the fifth and ninth day, as a prophylactic.

I do approve most heartily of the wonderful experiments and preoperative observations which have been suggested and performed by Doctor Bancroft and his associates.

DR. MARGARET STANLEY-BROWN (New York) closing: I would like to show you the way in which we obtain our plasma clotting index. The normal time for plasma clotting is one minute and 45 seconds, but it is a little complicated to talk about any factor in minutes and seconds, so we reduce that factor into seconds, using that which is our average normal as our numerator and the patient's plasma clotting time in seconds as the denominator. The result is what we term our plasma clotting index, and that is the term we use when we are speaking of this test. The normal plasma clotting time runs anywhere between 0.8 and 1.05 minutes. Anything below 0.8 we consider as potential bleeders, and above 1.05 as potential clotters. Fibrinogen over 0.7 per cent suggests infection or periphlebitis.

THE TREATMENT OF EMBOLISM OF THE GREATER ARTERIES

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AFTER Key[1] popularized the operation of embolectomy it became generally an accepted and somewhat spectacular procedure in the treatment of acute arterial embolism. From the time of Key's paper until recently it was the only active treatment considered to be of real value by those who have made a special study of this condition. To prove its value it was merely necessary to show that patients who had had the operation performed properly at the proper time suffered less frequently from gangrene of the affected limb, and that the mortality was at least no greater than that among patients receiving expectant treatment together with any necessary amputation. Two really comparable groups of patients thus treated have never been recorded, but the course of events in the patients who have been operated upon is so striking that observers are convinced that the operation is an important contribution to surgical practice.

Recently, two new nonoperative procedures and one new operation have come into use with claims made for them that results can be secured that are at least as good as, if not better than, those following embolectomy. These procedures are: (1) The use of a pulsating negative pressure pump,[2] to stimulate the circulation in the affected limb; (2) the use of an antispasmodic drug,[3] to overcome the immediate arterial spasm that follows the lodgment of the embolus; and (3) the operation of arteriectomy,[4] performed when a leg is affected in conjunction with procaine anesthetization of the lumbar sympathetics.

In order to determine the best treatment or combination of treatments among these suggestions, it is important to study the results of any considerable series of cases treated by any of these methods. Such series have been already reported for the operation of embolectomy, and recent useful reviews of the literature on this subject have been made by Key,[1] Pearse,[5] and Danzis.[6] Two articles concerned with the remote results following many hundreds of operations have recently been published by Strombeck,[7] and Hindmarsh and Sandberg.[8] Several more recent reports have appeared concerned with smaller series of cases, but they show no important variation from the treatment and results presented in the above mentioned articles. The present communication is concerned in part with a large personal series of cases for the most part treated by embolectomy, and brings out certain features of the problem not previously emphasized.

The Causes of Embolism.—Because an embolus is a solid mass floating in the blood stream, a discussion of its causation should be considered from

two points of view. The primary or predisposing factor is the cause of the solid mass in its original location. Cases of introduced foreign bodies such as bullets and instances of air, gas, or oil embolism will not be considered. Many more cases of thrombosis in vessels occur than are ever followed by embolism. Therefore there must also be an immediate cause that results in the freeing of the clot or plaque which allows it to become free in the blood stream. This immediate cause cannot always be discovered, but at times it seems to be directly connected with exercise and increased flow of blood from the legs in the case of emboli arising in the peripheral veins and at other times to reëstablishment of normal contractions in an auricle that has been paralyzed during a period of fibrillation.

Emboli that lodge in peripheral arteries usually arise in three places: First, in the wall of an artery, or in an aneurysm above the point of lodgment. These are not common. Second, in the left side of the heart. These are the most common. They may be associated with any type or stage of heart disease, but are especially common in cases with auricular fibrillation. Clots also frequently form on the inner surface of the ventricle in association with areas of infarction. The third source of emboli is in the pulmonary veins. Pulmonary phlebitis is not a common condition, but does occur occasionally in cases of pulmonary abscess and other infectious processes.

Paradoxical Emboli.—The three sources mentioned in the last paragraph are the only possible sources of emboli unless there is an abnormal opening in the heart. The most common abnormality of this kind is a patent foramen ovale. In connection with this deformity a few cases of lodgment of emboli in peripheral arteries have been studied. These are called paradoxical emboli. Such emboli can arise only in the peripheral venous system or in the right auricle. Emboli arising in these locations nearly always pass directly through the heart into the pulmonary arteries. In fact they usually can pass only in this way because the pressures in the two auricles are so nearly equal that no current normally flows from one to the other even in the presence of a large opening between the two. But there are two sets of conditions that will cause a relatively higher pressure on the right side and therefore determine a shunt from the right to the left auricle. These are: First, stenosis or incompetence of the bicuspid valves or stenosis of the pulmonary valves; and second, damming up of the blood in the pulmonary arteries following the lodgment of a pulmonary embolus. The first class of these causes is so rare that it does not need to be discussed, but the second is an associated cause in nearly all paradoxical emboli. This association has also caused much confusion in the consideration of the whole problem. The occurrence of a paradoxical embolism, then, practically presupposes that two separate emboli have been dislodged from the peripheral venous bed, the first lodging normally in the pulmonary arteries and the second, as a result of relative right-sided cardiac failure,

being shunted through an open foramen ovale to the left auricle and then to the greater arterial tree.

This conception is found in the continental literature.[1 (b)] It has not come to the author's attention while reviewing the literature except in the recent article by Hirschboeck[9] who does not quote from Key.

The Lodgment of the Embolus.—The point of lodgment of an embolus will necessarily be that point in the arterial tree that the embolus reaches that is too small for it to pass through. Depending upon its size it may happen to lodge in any branch in the arterial tree. Because points of narrowing of arteries are rarely found except at branches, an embolus will nearly always be found to lodge at such a point and will usually plug both the branches.

Emboli lodging at points other than branches of arteries are probably most frequently caught in the heart itself. In one of the cases in the present series there was a large embolus that arose in the left auricle, moved into the blood stream and caught in the narrowed mitral valve, resulting in immediate death.

A point in relation to the lodgment and effects of embolism that has not been sufficiently studied in the past concerns the relationship of the physical consistency of the embolus to its effects. Some emboli are well organized or otherwise firm clots, or are even hard arteriosclerotic plaques. Others, however, are very soft, mushy clots, not at all organized. These may represent clots that have become dislodged almost immediately after they began to form, before the fibrin had retracted. When the former type of clot lodges it will remain in one piece and will plug not more than the main artery and one branch, unless the clot is very long in comparison with its diameter. The other type, however, will run down an artery, break up on striking an obstruction and may, in some cases, plug any number of branches as well as the main arterial channel (Kohlmayer[3]).

Effects of Embolism.—The effect of an embolism is to decrease the arterial blood supply to the area served by the artery or arteries involved. In the case of an end-artery without important collaterals, the result may be immediate and complete gangrene of the tissue or organ. In most situations, however, the effect is a relative rather than absolute one, the degree of impairment of the blood flow varying with the efficiency of the collateral circulation.

The development of collateral circulation is influenced by many factors, all of which should be considered in any given case, but many of which are frequently forgotten. These are:

(1) The General Circulatory Efficiency and Reserve: The results of arterial ligations in healthy people would show a definite difference from the results in people with impaired cardiovascular apparatus. Lowered pulse pressure and blood flow alone can easily be seen to militate against the delivering of sufficient blood to a tissue through the circuitous route of collateral channels. As with all subsequent factors discussed, however, the difference is quantitative rather than qualitative and some circulation

can always be delivered below a point of blockage as long as a patient is alive. At times this circulation may be surprisingly good in spite of an apparently very much crippled heart.

(2) The Elasticity of the Vessels: Collateral circulation through arteriosclerotic vessels is never as good as through normal ones for the same reasons and to the same extent that straight circulation is impaired. Inasmuch as a fair number of these emboli occur in such cases, this factor must be considered.

(3) The Degree, Extent, and Duration of Spasm in the Arterial Tree: When an embolus lodges, the first reaction is an intense spasm of the arterial tree in the whole region supplied by the vessel. This reflex may represent an effort to maintain pressure in the vessels affected. Its continuance, however, may have the deleterious effect of retarding the dilatation of adequate collateral channels. It is to attempt to correct this situation that antispasmodic drugs are given. In any case the spasm passes off after a shorter or longer period of time. The intensity and duration of the spasm are variable and enter into the picture and the prognosis of all these cases.

(4) The Anatomic Arrangement of the Vessels: Embolism and ligation of corresponding points on the arterial tree of the arm and the leg result in much more serious effects to the leg. For some reason the collateral channels to the arms are much more efficient than those of the legs. Emboli or ligature of renal and large branches of mesenteric vessels and some others produce an ischemia that can never be taken care of by collateral circulation. This is also seen rarely when there is a developmental defect of one of a pair of arteries, for instance, an ulna artery occluded in a case with an absent or very small radial.

(5) Previous Pathologic or Other Occlusions: At times a small embolus lodging in a vessel that could usually be considered dispensable will result in death of a part. Such a situation is seen in the lodging of an embolus in the dorsalis pedis artery when the posterior tibial has been previously occluded.

(6) The Number of Channels Blocked by the Immediate Embolus: This subject was mentioned above in regard to the consistency of the clot. In Case 22, there was a large soft clot that apparently filled the whole brachial artery from high in the axilla to below the bifurcation of the radial and ulna. This was not a secondary thrombosis, but the original embolus. This situation was not entirely appraised at operation and if it had been it would have been impossible to meet it adequately. The result was gangrene well above the elbow, a situation that is very rare in embolism of the upper extremity. Every vessel occluded below the uppermost makes the possible collateral channel more devious so that the factor of blocking more than one branch is of the greatest importance in the understanding of these cases.

(7) The Size of the Vessel Involved: It was formerly believed that high ligations were more dangerous from the standpoint of gangrene than lower

ones. At present it is quite generally appreciated that this is not true. In respect to embolism the blocking of the bifurcation of the popliteal into anterior and posterior tibial arteries is the most dangerous to the foot. As one ascends the femoral and iliacs, the blocking of no single higher bifurcation is followed on the average by as extensive gangrene.

Embolism and Thrombosis.—Authors concerned with arterial disease frequently have much difficulty in classifying these cases into those in which embolism was the cause of a thrombosis and those in which the thrombosis was spontaneous, or at least caused by nothing more evident than spasm or a slight rupture of the intima. In respect to Buerger's disease, occlusions of the coronary vessels and other vessels of this size or smaller, there is no doubt that embolism is highly unimportant as a cause of occlusions. But in occlusion of greater vessels, popliteal to aorta and cubital to aorta, some pathologists[11] think that thrombosis without embolism practically never occurs. In the large series of cases operated upon in Sweden,[7, 8] which now amount to 367, an embolus is practically always located at operation when embolism has been the preoperative diagnosis, and all cases of acute major peripheral artery occlusion are operated upon under this diagnosis if they are seen in time. In our own series the same results obtain. On the other hand, in a recent report by McKechnie and Allen,[11] they attempted to divide the 100 cases observed into the two classes of embolism and thrombosis. They stated that this was difficult and not entirely satisfactory. Herrman and Reid[2] also reserve this diagnosis for the late neglected patient who comes in with the circulation so impaired that gangrene is either present or inevitable. From our experience with many such cases observed, and a few of them operated upon or examined postmortem, we believe that in well over 90 per cent a major embolus was the initial cause of the gangrene. It is freely admitted that thrombosis is also present in neglected cases. But this is the secondary thrombus that begins to form in from six to 12 hours following the lodgment of an embolus if the embolus is neither removed nor otherwise adequately treated.

The Results of Treatment of Acute Embolism by Operation.—The first operation of embolectomy at the Boston City Hospital was performed by I. J. Walker, in 1925. Several other cases were operated upon between that time and the first case of the author's, in 1929. These were reported in detail in 1931.[12] The present study includes all the cases on whom a final diagnosis of major peripheral emoblism or thrombosis was made at the hospital from the time of the author's first case through the year 1935, except that cases with a duration of over one week from the onset before being admitted to the hospital were eliminated. Two additional cases from the author's practice have been added. In addition to Case 1, Case 7 has been previously reported.[13] All cases of cerebral, coronary, pulmonary and abdominal embolism have been eliminated from the study.

During this period of just under seven years, 55 diagnoses of peripheral

arterial embolism and thrombosis have been made. On 27 of them arterial operations have been performed. Due to the kindness of his colleagues the author has performed most of these operations (Table I).

TABLE I

ARTERIAL OPERATIONS FOR EMBOLISM

	Single Embolectomy	Bilateral Embolectomy	Exploration	Ligations	Total Arteries Operated Upon
Author.....	15	2	2	1	22
Author's service.	5	0	0	0	5
Other services...	3	0	0	0	3
Total.....	23	2	2	1	30

The results of these operations will be seen in Table II. In constructing this tabulation, figures are incorporated for comparison that are taken from Strombeck,[7] and Hindmarsh and Sandberg.[8] These tables present operative results in the most clear cut manner that has been used for any large series of cases. Our statistics seem small when put beside Key's personal cases and especially small when compared to the total Swedish experience, but so far as the author knows, it represents the largest reported experience of any hospital outside of Sweden.

TABLE II

RESULTS OF EMBOLECTOMY

(*Classified as in Papers in Acta Chirurgica, 1935*)

	Number of Cases				Mortality Percentage	Percentage of Success
	Discharged Alive		Died in Hospital	Total		
	With Good Circulation	After Amputation				
Total Swedish experience except Key's.....	61	59	207	327	63%	19%
Key.....	17	10	18	45	40%	38%
Boston City Hospital....	10	5	12	27	44%	37%

A number of the patients who died in the hospital died in spite of the fact that complete relief of the circulation to the limb had followed the operation. Although these patients died, tabulation purely on the basis of local result helps to show the true picture of the technical possibilities of the operation.

TABLE III

LOCAL RESULT OF EMBOLECTOMY

	Adequate Local Circulation	Indeterminate*	Gangrene†	Total Determinate	Percentage of Adequate Local Circulation Determinate
Arms	6	0	1	7	86%
Legs (not cases)	9	4	10	19	48%
Total	15	4	11	26	58%

* This means death in 48 hours no matter how good the circulation in the limb seemed to be.

† Includes two patients that died following infection, one from the results of a burn and one of secondary hemorrhage from infection of the embolectomy wound. Neither actually had appreciable gangrene, but both had somewhat impaired circulation.

Table III shows an astoundingly high percentage of good local results following embolectomy of the arm. This will be discussed later.

Unfortunately the Swedish articles quoted in Table II do not separate the cases operated upon in the early years of the procedure from those operated upon more recently, so that they do not indicate any improvement from better selection of operative material as experience has been gained. Inasmuch as striking improvement occurred in our series, some data on this point may be of interest. At first, a few operations were performed upon patients in whom embolism had occurred 24 hours or more before operation in the hope that some partial success might allow a lower amputation than would otherwise be obtained. Occasional good results up to 24 hours had been reported by many authors. This study shows that no results of any use have been obtained in cases operated upon more than nine hours after the embolism. We realized, in 1932, that this was approximately true, and therefore largely gave up operating upon any late cases after this time. Table IV shows the duration of the embolism to operation in this series divided into an earlier and a later period. It explains part, but not all, of the improvement shown in

TABLE IV

DURATION FROM EMBOLISM TO OPERATION

	Up to 4 hrs.	4 to 9 hrs.	12 hrs. and over
1929–1932	3	4	4
1933–1935	6	9	1

Note: There were no cases giving duration between nine and 12 hours.

Table V. Additional improvement in results came from better technical surgery, judgment, and after-care.

TABLE V

RESULTS OF EMBOLECTOMY

Improvement in Results Dependent upon Experience

	Number of Cases					
	Discharged Alive					
	With Good Circulation	After Amputation	Died in Hospital	Total	Mortality Percentage	Percentage of Success
1929–1932	3	1	8	12	67%	25%
1933–1935	7	4	4	15	27%	46%
Total	10	5	12	27	44%	37%

Embolism of the Arm Versus Embolism of the Leg.—It has been recognized for a long time that particularly favorable local results followed operations for emboli of the upper extremities compared to those of the legs. In this series there were seven such operations on the arm. Table VI includes the Boston City Hospital cases in Table II and divides them according to location.

TABLE VI

RESULTS OF EMBOLECTOMY

Upper and Lower Limbs

	Number of Cases					
	Discharged Alive					
	With Good Circulation	After Amputation	Died in Hospital	Total	Mortality Percentage	Percentage of Success
Arms	3	1	3	7	43%	43%
Legs	7*	4	9	20	45%	35%
Total	10	5	12	27	44%	37%

* One bilateral case was counted once only and one case with two successive operations counted once only.

Table VI does not show it, but all three of the patients with axillary or brachial embolism who died were relieved locally. It is seen that when

the cases are presented in this way, the inclusion of a number of the favorable upper extremity cases did not make our total results more favorable to a statistically significant degree.

Inasmuch as there is a marked difference in the local results of embolism of the legs from the results in the upper extremity, further discussion is necessary. The matter of axillary and brachial operations will be discussed in a later section after the results of nonoperative treatment have been presented. Table VII shows the results of operations upon the leg arteries divided into an earlier and a later period, as was done in Table V, for the whole series. This is done with the full realization that this subdivision makes the totals smaller and therefore increases the statistical error and makes conclusions drawn from slight differences in percentage to be of no value.

TABLE VII

RESULTS OF EMBOLECTOMY

Legs Only—Improvement with Experience

	Number of Cases					
	Discharged Alive					
	With Good Circulation	After Amputation	Died in Hospital	Total	Mortality Percentage	Percentage of Success
1929–1932	2*	2	7	11	64%	18%
1933–1935	5†	2	2	9	22%	55%
Total	7	4	9	20	45%	35%

*One case bilateral, counted once only.

†One case, two successive operations without death or gangrene, counted once only.

Table VII shows a very marked improvement in results after experience in management and selection had been gained.

The Results of Treatment of Embolism in Cases That Did Not Have Embolectomy.—In considering the cases to be presented in this category, it must be remembered that most of them were treated before the possibilities of passive vascular exercises, drug treatment, or the dangers of heat had been demonstrated. Only a few of them came to the attention of the author during their lives and they were widely distributed over all the services of the hospital. The scattering was so great that, on the average, no one service saw more than one case in two years. It also is of note that cases of this type have seldom, if ever, been carefully studied, in modern times, separate from the other, less sudden and complete types of arterial obstruction and limited to the occlusions of the major arteries rather than

of the arterioles. When major occlusion occurs in cases which are already in partial or complete cardiac failure, and who have added to this a great deal of pain and the toxemia of the dissolution of large masses of tissue, the result can only be that the patient's condition becomes desperate. Just when the optimum time for amputation is reached is difficult to know when it is present and impossible to predict.

There were 29 cases in this group that did not have any operative attempt to clear their arteries. The results obtained in this group have been tabulated in the same way as were the operative cases (Table VIII).

TABLE VIII

RESULTS IN CASES OF EMBOLI NOT HAVING HAD ARTERIAL OPERATIONS

	Number of Cases Discharged Alive					
	With Good Circulation	After Amputation	Died in Hospital	Total	Mortality Percentage	Percentage of Success
Arms	1	0	6	7	86%	14%
Legs	2*	3*	18	22	75%	8%
Total	3*	3*	24	29	85%	8%

* One patient with bilateral emboli who lost only one leg counted in both columns, but not in vertical total.

These results are appalling. They also show that, in relation to the chance of the patient's survival, embolism of the arm is neither less serious nor occurs in less seriously ill cases, than does embolism of the legs. Table IX will show, however, that there is a distinctly more favorable outlook as far as gangrene is concerned in arm cases, as distinguished from leg cases.

Table IX when compared to Table III shows clearly that embolectomy plays no part in preventing gangrene from occuring following embolism of

TABLE IX

LOCAL RESULTS OF EMBOLISM NOT OPERATED UPON

	Adequate Local Circulation	Indeterminate	Gangrene	Total Determinate	Percentage of Adequate Local Circulation
Arms	5	2	0	5	100%
Legs (not cases)	4	3	16	20	20%
Total	9	5	16	25	36%

the arteries to the arm. The only case in this extremity among the ten determinate cases that resulted in gangrene was Case 22. Her embolus was of such a nature that surgery could not possibly relieve it. The number of arm cases studied seems to us to be large enough to state quite positively that embolectomy is not necessary or desirable in any cases of embolism of the major arteries of the upper extremity.

When gangrene has become established in cases of embolism, there are many physicians and surgeons who look at the patient's condition as so desperate that they procrastinate, hoping for a change for the better in the patient's condition. The patients that had an embolectomy that failed were, for the most part, amputated within a few days (Table X).

TABLE X

AMPUTATION IN THE TREATMENT OF POSTEMBOLECTOMY GANGRENE

	Amputation		No Amputation	Total	Percentage of Amputation to Gangrene	Mortality Percentage
	Lived	Died	Died			
Arms	1	0	0	1	100%	0%
Legs (not cases)	4	5	1	10	90%	60%
Total	5	5	1	11	91%	54%

The patients that did not have an attempt at embolectomy were not amputated nearly so promptly. In fact some went on to death at the end of periods of two to four weeks without ever having an amputation (Table XI). (In many of these cases this was not the fault of the surgeon, as amputation was refused by the patient or his family.)

TABLE XI

AMPUTATION FOR GANGRENE IN CASES WITHOUT EMBOLECTOMY

Indeterminate Cases Excluded

	Amputation		No Amputation	Total	Percentage of Amputation to Gangrene	Mortality
	Lived	Died	Died			
Arms	0	0	0	0	—	—
Legs	3	5	8	16	50%	81%

Compared to Table X, Table XI shows a much lower per cent of cases operated upon. Of those which were amputated the survivals were 37 per cent compared to 50 per cent. In the whole group the survivals were 19 and 46 per cent respectively. It is believed that these figures tend to show

that rather prompt amputation after the establishment of gangrene is important.

SUMMARY AND CONCLUSIONS

(1) Fifty-five cases of major arterial embolism have been presented with respect to their condition at the time of discharge from the hospital.

(2) After experience had been gained, quite good results followed the operation of embolectomy when performed early on the arteries of the leg.

(3) No benefit is gained by such operations on the upper extremity.

(4) Embolism of the upper extremity, as distinguished from that of the lower, very seldom leads to gangrene.

(5) Cases that did not have embolectomy nearly all died whether or not there was gangrene or amputation.

ABBREVIATED CASE REPORTS OF 55 PATIENTS UPON WHOM DIAGNOSES HAVE BEEN MADE OF PERIPHERAL ARTERIAL EMBOLISM AND THROMBOSIS, FROM WHICH DATA THIS ARTICLE HAS BEEN DEVELOPED

Case 1.*—F. G., male, age 78. Admitted March 26, 1929, to Fifth Surgical Service. He came to the hospital because of precordial pain, cough and dyspnea that he had had for several years. While being examined in the admitting room, he had a sudden severe pain in the right arm and hand. He showed emaciation, cyanosis and respiratory distress. The heart was slightly enlarged and its rhythm entirely irregular. The peripheral vessels were markedly sclerotic. There were dulness and crepitant râles at both bases. The right radial and brachial pulses were absent, but pulsation could be felt high in the axilla down to a point of thickening in the artery where it stopped abruptly. The forearm and hand shortly became cold, cyanotic and paralyzed.

Operation was performed two hours after the onset of the symptoms. Under procaine, with the patient sitting on a chair, because of his acute heart failure, the artery was opened over the bulge, after isolating it and controlling it above by a loop of heavy catgut placed as a tractor, and after applying Crile clamps to the main artery and profunda branch below, the clot was partly expressed by manipulation and completely expressed by allowing a momentary spurt of blood. The radial artery was then exposed and salt solution injected into it through a large caliber needle. It was thought that a small fragment of clot was washed out from below by this procedure. In any event there was good collateral bleeding from the artery in this direction and also from the profunda. The incision in the artery was then closed with fine silk sutures soaked in Vaseline.

The local result of the operation was perfect. There was immediate return of blood to the arm, the hand became warm and the paralysis was cleared by morning. The radial pulse was palpable the next day. After a week the patient began to get out of bed, notwithstanding his serious heart condition, chronic bronchitis and extreme weakness. He was transferred to the Medical Service where he gradually went down hill and died 13 weeks after the operation. There was no disability of the hand or arm at any time.

An autopsy was performed which showed syphlitic aortitis, generalized arteriosclerosis, cardiac dilatation, fibrous pleuritis and old infarcts in the right lower lobe of the lung. The aorta was dilated and tortuous and contained many ulcerating, fungating vegetations. Unfortunately the death and autopsy did not come immediately to the attention of the Surgical Service and the pathologist did not realize our interest in the healing of the surgical wound. No specimen of this was obtained.

Case 2.—J. T., female, age 51. Admitted March 28, 1929, to the Second Medical

* This case has been previously reported.[19]

Service. Twelve hours previously she had suffered a sudden left hemiplegia. She showed fibrillation and no pulse in right arm. After the ninth day the pulse began to return in the arm. No gangrene had developed. The hemiplegia began to clear. Patient then developed phlebitis of both legs. After 12 weeks in the hospital she had another cerebral accident and died three days later.

Case 3.—M. K., female, age 75. Admitted July 5, 1929, to the Fourth Surgical Service. She came in with an acute gallbladder attack. At an emergency operation a stone was removed and the gallbladder drained. She had auricular fibrillation during her entire hospitalization. On July 11, absent radial pulse with weak pulse at elbow was noticed. The duration was uncertain.

At operation an incision at the junction of the brachial and axillary arteries was made. The artery was exposed, suspended, incised and the clot removed. Further clots were secured by washing saline upward from the wrist. The wound in the artery was closed with interrupted silk. Two days later the radial pulse was felt and the hand was warm. The fingers were still slightly cyanotic. On the fourth day she became delirious and died suddenly.

Case 4.—M. H., female, age 75. Admitted July 17, 1929, to the Fourth Surgical Service. She had been on the Second Medical Service for treatment of heart failure and fibrillation. Twenty-four hours previously she had had sudden pain in the right ankle and foot, and foot became cold. At 6:00 A.M. on July 17, she had sudden pain in right thigh and the whole leg became cold. It was discolored up to four inches below Poupart's ligament.

At operation a vertical incision was made up the leg. The femoral artery was exposed and no pulsation found. Incision extended up to the external iliac where pulsation was obtained. Femoral vein was separated from the artery and double catgut passed around the artery to control hemorrhage. Artery split longitudinally and clot shelled out. Femoral artery milked upward and more clot obtained. Artery sutured with Vaseline sutures. The following day, pulsation was felt. Ecchymosis fading down to two inches below the knee. Condition was fair although fibrillating. The same afternoon the patient died suddenly.

Case 5.—H. R., male, age 60. Admitted January 6, 1930, to the Second Medical Service. Came in alcoholic and with delirium tremens and nearly died of it. On January 19, it was noticed that the right leg was gangrenous. No history or knowledge as to the length of time it had been developing. On January 21, transferred to the Third Surgical Service and thigh amputation performed. Death two days later. Medicolegal autopsy showed thrombosis of artery and vein, and terminal pneumonia.

Case 6.—M. C., female, age 71. Admitted February 13, 1930, to First Surgical Service. Two days previously had noticed cold and numbness of the left arm and hand. This became progressively worse. On examination had fibrillation, the hand and forearm were cold and cyanotic and somewhat anesthetic. No radial or brachial pulse. Faint pulsation in axilla.

At operation an axillary incision was made. The vessel was exposed and controlled with rubber traction tube. Opened just below end of pulsation. Small soft clot 2 cm. long was removed. No bleeding from below. Radial opened and found to bleed a little, and salt solution injected upward with release of small amount of clot. Wound closed with silk.

Postoperative Course.—Patient did well. Circulation returned slowly to arm. No gangrene. On February 28, patient died very suddenly when out of bed for the second time.

Case 7.*—R. S., female, age 34. Admitted June 6, 1930, to the Fourth Medical Service, suffering from sore throat, fever, and recurrent generalized "rheumatism." Fifteen years before she had been in a hospital for six weeks with "rheumatism" and been told then that she had some heart trouble. She had, however, had no cardiac symptoms until the present illness. Examination showed a fairly well developed and well nourished woman

* This case has been previously reported.[13]

sitting up in bed with slightly labored respiration, but not cyanotic. The heart was greatly enlarged, and the sounds totally irregular. Pulse, 130-150. Liver enlarged. A roentgenogram showed "typical mitral heart." During the 12 days in the hospital she improved steadily, the temperature and pulse coming down and the pains diminishing. The pulse remained irregular. Digitalis was given.

About 5:00 A.M. on June 18, she felt a severe pain like an "electric" shock in both legs, especially below the knees. The intern was not called. During the next few hours the left leg became more comfortable, but the right remained painful and then became numb. On examination later in the morning, she showed pallor and coldness of both legs, especially marked below the right knee. Pulsation could not be felt in either dorsalis pedis, posterior tibial or popliteal artery, or in the right femoral. She was given morphine and scopolamin, transferred to the Fifth Surgical Service, and sent to the operating room. Although in good condition when she left the ward, five minutes later, on arrival, she seemed to be dying. She was cyanotic, gasping for breath and unconscious. Her pulse was barely palpable, somewhere over 160. There were coarse bubbling râles at both bases. The veins in her neck were greatly distended and pulsating widely. She was given caffeine and atropine without effect. The lungs continued to fill so that froth began to come out of her nose. At this point a venesection was suggested by the surgical resident, and 700 cc. of blood withdrawn. This took about 15 minutes; at the end of this time she began to breathe a little better. After another hour she was definitely better. It was felt that she might survive the attack of pulmonary edema and that the operation had better be performed.

Operation.—Time, 2:00 P.M. The patient was placed in a semireclining position. Under local anesthesia the right femoral artery was exposed at the point of the profunda branch. A firm mass could be felt in the artery at this point, but no downward thrust. Below this point it was greatly contracted. After isolating the artery, it was controlled with catheters and opened over the clot which was extruded. There was then good back bleeding from the two distal arteries, but no proximal bleeding. A uterine probe was then passed up its lumen but nothing was dislodged. Following this, a vein stripper with a medium sized tip was passed up it a distance of 20 cm. and on withdrawal a few fragments of clot came out, being washed by a fair stream of blood. The blood came with enough force to make a spurt about one inch high. The artery was then closed and it was seen that the stream of blood was not forceful enough to produce any visible or palpable pulsation on the exposed artery. It was then opened again just below the previous incision, being controlled as before. The left femoral artery was then exposed, dissected out, controlled and opened. This artery was contracted, not pulsating, and no clot could be felt at the branch. After opening it, a uterine probe was passed up about 10 cm., when there was a sudden vigorous gush of large clots and blood. The flow was controlled at once by lifting on the catheter and the other side was probed again. Both sides were probed in turn the full length of the probes and for 30 cm. with the vein stripper, but no more firm clot could be recovered. A small, very soft fresh clot was secured from the right femoral which continued to emit the same slow flow of blood, but its force could not be improved. It was then decided that we had been working long enough and both arteries were sutured and the wound closed. Both legs were wrapped in large amounts of cotton wadding and the patient was returned to the ward.

Heat was applied to the legs by means of an electric bulb suspended from a cradle. The patient's general condition improved during the operation, but she had not recovered from her coma at the end of it. On arrival in the ward her lungs were clear of râles except at the extreme bases. In the evening she was conscious and looked better, and pulsation could be felt in the left dorsalis pedis artery.

June 19: The left leg and foot were absolutely normal and remained so the rest of the stay in the hospital. They were warm and pink and pulsations were present in the dorsalis pedis, popliteal and femoral arteries. There was no pain and motions were all normal. The right leg was warmer and not so dead white as before operation, but no

pulsation could be felt at any point. She could, however, move her toes and foot a little, and she had only slight pain.

The circulation in the right leg improved very slowly but steadily. The patient had cramps in the calf that were troublesome and for a long time the muscles were very weak. The leg was kept warm constantly. On the fourth day after operation she had a sudden rise in temperature to 102° F., associated with cough. There were showers of crepitating to consonating râles throughout the lower third of the right chest. The wounds were clean. A roentgenogram of the chest (portable) showed enlargement of the heart and a cloudy patch of increased density in the left midchest with a thickened interlobar septum above it. Bronchopneumonia was the tentative diagnosis. The chest condition cleared slowly and was apparently normal at the end of two weeks. At the end of four weeks physiotherapy was started, but the patient could stand very little massage as it would induce cramps. At the end of three weeks she began to sit up in a chair. The patient was demonstrated at this time before a meeting of the New England Surgical Society, when she showed a normal circulation in the left leg and an almost normal circulation in the right, without, however, any pulsation along the course of the main artery on the right. She was able to walk as well as her heart would permit her to.

Seven months after this embolism she suffered from another, for which she was treated in the hospital. This was located in the right cerebrum. No operation was performed. The end-result of this second embolic accident was a permanent spasticity of the left arm and leg. She continued to suffer occasional attacks of cardiac decompensation for which she was admitted to the hospital, and was last seen in July, 1935. Since the cerebral accident there have been no further emboli. She is able to walk, as far as the condition of her heart will permit, in spite of the remaining spasticity in her left leg.

Case 8.—P. McD., male, age 75. Admitted June 10, 1929, to the Fifth Medical Service, complaining of attacks of dizziness and weakness of five days' duration. After admission the patient developed pneumonia and was fibrillating. He was digitalized. On the ninth day he suffered a sudden pain in the right leg from the hip down and the leg became cold and cyanotic. The dorsalis pedis pulse could not be felt and the popliteal pulse was weak on this side. A surgical resident saw him and advised against operation. Gangrene developed and he died seven days later. At no time did his general condition seem to warrant amputation.

Case 9.—J. H., female, age 60. Admitted June 5, 1930, to the Second Medical Service, complaining of cough, orthopnea, and edema of several weeks' duration. She had had rheumatic fever 36 years before. On admission her heart was enlarged and its action irregular from coupled beats. Her blood pressure was 216/120. She was quite obese. She improved rapidly with rest in bed and digitalis, and after three days was allowed out of bed. On the second day up she had a sudden attack of generalized abdominal pain and vomiting. On examination there was no spasm or tenderness. Her temperature was normal, and no surgical "visiting man" was called. The abdominal pain continued and two days later it was noted that the left foot was very cyanotic and that no pulse could be felt in the dorsalis pedis, popliteal or femoral arteries on that side. The abdomen was slightly distended and generally tender. It was felt that there had been an embolism in a branch of the mesenteric artery, but that it had not been extensive enough to warrant abdominal exploration. The patient was taken to the operating room where the left femoral artery was exposed and found to be pulsating normally, but weakly. The incision was closed. The patient died 12 hours later.

Autopsy showed embolism of the superior mesenteric artery with gangrene of the whole small intestine and the right half of the colon.

Case 10.—C. R., male, age 52. Admitted October 24, 1930, to the Second Medical Service, presenting phenomena of cardiac decompensation, hypertension and fibrillation. Two days before admission he had had a sudden pain in the right popliteal space. No pulse was felt in the left popliteal or foot. In the next five days definite gangrene of

the foot developed. On October 29, he was seen by a surgeon who did not believe his condition warranted amputation, and the femoral vein alone was ligated. He died six days later of hypertensive heart disease and gangrene of the leg.

Case 11.—E. O H., female, age 39. Admitted to the Fifth Medical Service, February 9, 1931. After being in bed with the "grippe" for a day, she had suddenly, three days before admission, experienced a sharp pain in her legs. She was given some medicine for the pain and hot water bottles were applied to her legs. She lost sensation in her legs and as a result suffered a severe burn in the right calf; she also stated that her toes had become black before she entered the hospital. On examination all pulsations in both legs were absent and there was gangrene established in the right foot. There was also a burn on the left calf. The heart was enlarged and fibrillating and showed evidence of severe mitral disease. She was started on a course of digitalis. She was seen by an attending surgeon on the morning of admission who felt that although operation was indicated, he was doubtful of its result. She was transferred to the Fifth Surgical Service.

Operation.—Right inguinal incision. The lower iliac and upper femoral arteries were exposed and found to be not pulsating and full of clots. The vessel was opened and a large amount of old black clot was squeezed out, clearing the vessel. Various probes followed by vein strippers were introduced both upward and downward, cleansing the vessel from the aorta to the knee. The same operation was performed on the left side, with the same findings. The vessels were sutured with one row of sutures after injecting sodium citrate solution into their lumina.

The day after operation there was a definite pulsation in the left femoral, but none in the right or on either side at any lower point. The right leg became gangrenous and was amputated nine days later. The left leg remained alive, but painful, and the burn needed constant attention.

After several weeks she was transferred back to the Medical Service for treatment for her heart, with the burn on the left calf still not healed. The amputation stump was clean and healed. The circulation in the left leg improved very slowly. On April 26, she was sent back to the Surgical Service because of spreading sepsis from the burn. Several drainage operations were performed, but gangrene finally developed in this foot also and the leg was amputated on May 26. She withstood this operation well, was conscious and rational, and did not seem particularly sick. Suddenly on the fourth day while talking to a nurse she suddenly died.

At the autopsy her heart was found enlarged, especially the left auricle. The mitral valve was sclerosed so as to admit the tip of one finger only. A ball valve thrombus the size of a hen's egg lay in the right auricle. There was also a thrombus of the lower 5 cm. of the aorta and both iliacs. This was not recanalized on the left, but was recanalized on the right. The right common, external and femoral arteries showed two lumina.

Case 12.—E. J. V., male, age 48. Admitted February 10, 1931, to the Fifth Medical Service. After a period of ten days of drunkenness, he had noticed numbness of the right toes. Notwithstanding medical attention, his condition became gradually worse during the next three days. Examination showed the heart to be regular. The right foot was cyanotic to the ankle. The skin was dry and hard. The popliteal pulse was absent, but the femoral pulse was present.

The artery was exposed in the popliteal space and found to be patent to the middle of the space, but no lower. Incision was made over the clot, which was removed. Vein strippers were passed down the anterior tibial artery to the ankle, removing clots. Ten cubic centimeters of salt solution were injected down the artery, which was then sutured. Pulsation satisfactory after suture as far as could be felt in the wound. No reëstablishment of circulation postoperatively. Amputation February 28. Wound infection took place, but he recovered and the stump healed. Discharged, May 27.

Case 13.—M. J. W., female, age 81. Admitted to the Palmer Memorial Hospital,

May 20, 1931. About 2.00 P.M. on the afternoon of the day of admission, she had had a sudden sharp pain in the right calf. This rapidly increased to great severity. When her doctor arrived he found the leg cold, pale and with no pulse at the femoral or below. She had always been well and had led an active life until the last two years, when there occurred increasing dyspnea on exertion. Six months before, following a "cold," there had been a definite attack of heart failure with irregular pulse. Examination on admission, at 6:00 P.M., showed a thin, feeble, elderly woman in great pain. The knee was drawn up and the foot paralyzed. The leg was blanched, cold, and slightly tender. No pulses could be felt on this side although there was excellent pulsation in the other leg at all points where they were normally palpable. Her heart was enlarged. There was a soft systolic murmur. The rhythm was completely irregular.

Operation was performed at once, five hours after the onset. The femoral artery was found to be contracted and empty. Probing upward a short distance dislodged a medium sized soft clot followed by a tremendous spurt of blood. The wound in the artery was closed.

The next morning her foot and leg were practically normal. The femoral and popliteal pulsations were easily palpable, but not those of the foot. She was able to be out of bed in six days and walked out of the hospital with no disability in 16 days. She remained well until two years later when she died of acute appendicitis.

Case 14.—C. C., male, age 49. Admitted to the Fifth Surgical Service, June 9, 1931, complaining of hyperesthesia of the legs with cramps and weakness beginning the morning of entry. His history began three months before with a cellulitis of the right forearm. One month later he had a sudden cramp-like sensation around his right hip, which spread down to his ankle. This passed off gradually in the course of a month. One month ago he had had a sudden attack of asthma with wheezing orthopnea, dyspnea on climbing a flight of stairs with marked palpitation of the heart. No swelling of his ankles. Since then he has had similar paroxysms about three times a week. The day of entry he had been walking when he suddenly noticed a hyperesthesia of the left leg, which felt cold. There was also cramp-like pain beginning at the hip and extending downward. His leg became weak and he could not walk on it. In an hour the leg began to have clonic spasms and he was brought to the hospital.

Examination showed a well developed, poorly nourished white man. The lungs were clear and resonant except for wheezes just below the clavicle on both sides and some dulness at the right apex. There was a diastolic murmur heard at the apex of the heart. The blood pressure was 105/65. The left leg was colder than the right from the midthigh downward, and was much paler in general, but with bluish areas. All fingers showed marked clubbing.

Operation.—Upper left femoral incision, artery dissected out, found to be not pulsating. It was opened and two inches of soft clot removed, but without effecting release of the blood stream. Probing upward (several attempts), with the stripper, failed to clear the vessel, although it apparently passed an obstruction. By careful squeezing and pulling, eight inches of soft secondary clot were removed from below. Opening in the artery was closed with one layer of sutures. Incision extended upward, exposing profunda branch. Artery opened again and a small, firm, tough piece of tissue, lodged at this point, was squeezed out, which was followed by a free flow of blood. Artery sutured.

On account of the secondary clot, the patient was turned on his face and the popliteal space opened sufficiently to feel the popliteal artery beating well. Artery neither exposed nor cut. Incision closed.

Patient did very well the first few days, the circulation returned to the foot except in the great toe, and he recovered from the paralysis. On the fourth day his R.B.C. was 3,600,000 and W.B.C. 10,000. On the sixth day it was discovered that the wound in the groin was infected and some of the stitches were removed to secure drainage. The remainder were removed two days later. The infection evidently

spread during the next four days in spite of the drainage, as his temperature and pulse rate both increased. Dakin's dressings were applied but the inflammatory process continued in spite of treatment. On the 23rd day postoperative, there was a sudden severe secondary hemorrhage from the wound which, however, had ceased on arrival of the intern. He continued to have subsequent hemorrhages during the next few days in spite of packing and strapping the wound. On the 32nd day his wound was explored under anesthesia, after a transfusion of 500 cc. A small pocket of pus was found near the great vessels, but no bleeding point could be identified. Dependent drainage was provided and the wound packed and a tight dressing applied. The same afternoon he had another massive hemorrhage from which he died.

Autopsy.—Dry gangrene of distal 1 cm. of the left great toe. Multiple surgical wounds of the anterior left upper leg, with purulent discharge from them. Heart showed two grayish-white patches on anterior surface of the ventricle. Muscle very soft and flabby. Coronaries patent. Calcified plaques of aorta. Small aneurysm 0.5 cm. in diameter just above organized thrombus in femoral artery, 15 cm. below Poupart's. Small opening in aneurysm wall. No incision scar could be seen in femoral artery. Diagnoses: Acute vegetative endocarditis. Aneurysm of left femoral artery. Gangrene of left large toe. Syphilis of aorta. Bronchopneumonia.

Case 15.—M. M., female, age 41. Admitted August 28, 1931, to the Fifth Surgical Service. Two weeks before entry she had had a sudden pain in the right leg, which became cold and bluish. In two hours the pain disappeared, but the left leg became similarly affected, which phenomenon in turn, also disappeared. Seven hours before admission, patient suddenly had more pain in left leg which became white and cold, and then bluish. She was fibrillating. There was no pulse perceptible in the left femoral or below it.

At operation the femoral artery was exposed at the groin and opened. It was probed upward with return of four clots followed by a free flow of blood. The wound was closed with silk sutures. Gangrene developed. Amputation was performed seven days later.

September 16.—Sudden embolism of the right arm to the shoulder, the left arm to the elbow and of the aorta from which she succumbed the following day.

Case 16.—M. H., female, age 70. Admitted October 26, 1931, to the Fifth Surgical Service. Six hours before admission, had sudden numbness, pain, and coldness of right hand. Examination showed fibrillation, hand of dusky color, fingers stiff, radial pulse absent.

At operation the brachial artery was opened at the elbow. Five small clots were removed. Artery sutured with silk. Radial pulse was not restored. In spite of this the wound healed and the patient was discharged well and without gangrene.

Case 17.—B. S., female, age 59. Admitted to the Second Medical Service, February 12, 1932. She had been known to have had diabetes for some time. Chief complaints nausea, vomiting, and substernal pain. She was found to be fibrillating and to be decompensated. With rest in bed and other appropriate treatment she did very well. After four days she stopped fibrillating. The same afternoon she complained of sharp pain in the right leg. In one and one-half hours it increased steadily. When examined at that time the leg was found to be cold, the femoral pulse was present, but all pulses below were absent. The other leg was normal. She was again fibrillating. Blood pressure was 110/92. Transferred to the Fifth Surgical Service.

Operation.—The femoral and popliteal vessels were exposed and both found to be pulsating. The wounds were closed. The lower leg gradually became gangrenous with a line of demarcation just below the tibial tubercle. On February 27, a midthigh amputation was performed. The wound healed by first intention and the patient was transferred back to the Medical Service on April 11, where she died June 8, 1932, from heart failure. No autopsy.

Case 18.—M. B., female, age 39. Admitted March 9, 1932, to the First Medical

Service. She had had heart trouble for years, for which she had been treated. During the preceding week there had occurred increasing dyspnea. On the morning of admission she had fainted and subsequently noticed a severe pain in the right leg and foot, accompanied by numbness in the latter.

Examination showed fibrillation and purplish discoloration and coldness of the right foot. Right posterior tibia artery not palpable. No treatment to the leg. At the end of the third week there was well demarcated gangrene and amputation was advised. Transferred to the Fifth Surgical Service on April 8, 1932. Amputation was performed. C. welchii sepsis developed and she died four weeks later.

Autopsy showed mural thrombi 2x3 and 2x4 cm. in the left auricle, which projected into the narrowed opening of the mitral valve. Clots were found filling right iliac and femoral arteries and some smaller clots in the vessels on the left side. Thrombi were present in the abdominal aorta and left common iliac artery.

Case 19.—O. C., male, age 40. Admitted to the Third Medical Service, June 24, 1932. Dyspnea for one month and then nocturnal dyspnea for five days before admission. His extremities were normal and his heart regular on admission and remained regular. Electrocardiogram showed intraventricular block.

On July 8, he had a sudden steady pain in the left foot. After three hours the pain became worse and extended up to the knee. The leg became cold and pale. The dorsalis pedis and posterior tibia arteries could not be felt in either leg. The next day there was less pain, but the leg became blue and he could not move his toes. Later the leg showed dry gangrene. He died one month later without amputation, as his condition was considered to be too hazardous to allow of such a procedure.

Autopsy.—There was an old clot adherent over an infarct in posterolateral wall of the left ventricle. Valves were normal. There was an old thrombosis of descending branch of the right coronary artery. New thrombosis of the upper right coronary artery.

Case 20.—C. McD., female, age 49. Admitted to the Fourth Medical Service, August 25, 1932, complaining of dyspnea and palpitation of two months' duration. Ten years before had had dyspnea and edema that had been successfully treated. Since then she had had occasional mild attacks. She had rheumatic fever at the age of 14. On admission she had a temperature of 100° F., a pulse of 80, and respirations of 24. Her blood pressure was 100/40. She was able to lie flat in bed without distress. Her lungs showed slight dulness at the right base. Her heart was enlarged to the right and the left. There were systolic and diastolic murmurs at the left border of the sternum. The rhythm was completely irregular. There was pitting edema. She improved rapidly with digitalis and rest in bed. On September 8 she was allowed to get out of bed. The next day she had a sudden pain in the right leg about 4:00 A.M. She was seen six hours later, at which time the foot was cold and no vessels in the leg showed pulsation.

She was transferred to the Fifth Surgical Service. At operation the femoral artery was found to be contracted and not pulsating. It was opened and a vein stripper passed upward. Resistance was felt at about six inches. On breaking through this a large clot was dislodged and this was followed by normal bleeding. The vessel was closed by one layer of sutures.

She had no circulatory difficulty after operation and was able to walk easily on the twelfth day. On discharge at the end of 17 days all pulsations in the leg, foot and ankle were normal.

Case 21.—W. C., male, age 55. Admitted to the Dermatological Service, September 19, 1932. He came to the hospital very ill with a generalized eruption of his skin. A diagnosis of dermatitis exfoliativa was made. On the second day in the hospital while lying quietly in bed he felt a sudden sharp pain in the left groin. After this the leg became cold and began to tingle. Examination two hours after the onset showed pulsations absent in the whole left leg. He was transferred to the Fifth Surgical Service.

At operation the left femoral artery was exposed and found to be contracted and pulsating very weakly. On opening the vessel it was seen that the force of blood flow was way below normal. After probing upward a hard plaque was dislodged which was 2.0x0.5x0.2 cm. After this there was a good flow of blood. After the artery had been sutured the pulsations again became weak. The leg gradually became gangrenous to the knee, and the patient died on the sixth day postoperative. Amputation was not considered feasible because of the skin condition.

Case 22.—J. M. W., female, age 72. Admitted to the Newton Hospital, December 13, 1932. At noon on day of admission the patient had noticed a numb feeling and pain in the left arm. Her physician could make out no signs of any disability or find the cause of the pain. About one and one-half hours later she was seen again, at which time definite discoloration of the left arm and forearm and absence of the radial pulse were found. The pulse, however, could be felt in the axilla. Her heart was fibrillating, she was markedly dyspneic and looked as if she were dying of acute left-sided cardiac failure. During the afternoon she improved under treatment and was brought to the hospital at 8:30 P.M.

Examination showed lateral displacement of the left border of cardiac dulness and of the apex impulse. A systolic murmur was present over the whole precordium and totally irregular pulse. The left arm from just below the elbow was dusky and cold. No pulsation felt in any vessel below the axillary.

At operation the upper end of the brachial artery was exposed and found not to be pulsating. It was cleared for one inch at the level of the first main branches. Catheters were placed to control hemorrhage. It was opened and a small amount of soft clot expressed. This was followed by a copious flow of blood. While this was controlled by pull on the catheter the radial artery was exposed and needle inserted. No bleeding. Salt solution injected, but was followed by no flow of salt solution or blood from the lower end of the brachial. The artery was then closed with a single layer of continuous silk sutures and a small flow of arterial blood occurred from the needle at the wrist. The circulation was thought to be reëstablished. The wound was closed in layers. The arm was wrapped in cotton from the fingers to the shoulder.

The next day only slight pain was felt in the arm, which seemed less cold than before operation. Two days later there was severe pain, but the arm and hand looked fairly well. Until the fifth day the arm looked as though circulation would become reëstablished, but during the next two days definite gangrene with a line of demarcation above the elbow occurred. A high arm amputation was performed. Subsequent recovery uneventful.

Pathologic Report.—(1) "Embolus.—Three pieces of clot, the largest irregular in outline, measuring roughly 8x7x2 Mm. Microscopic examination shows laminated clot made up of layers of platelets in which are invading polymorphonuclear leukocytes and between these layers collections of red cells. The clot is more than one day old.

(2) "Arm.—Specimen consists of left arm, forearm and hand. It is amputated at approximately the junction of the first and second thirds. There is a distinct line of demarcation just above the elbow. The brachial artery was seen to be thrombosed in several places. Microscopic examination shows complete thrombus formation of the brachial artery; serial sections show the lumen of the artery to be constricted at the point of closure. It is probable that the repair of the incision aided in reformation of the thrombus."

Case 23.—H. R., female, age 36. Admitted to the Fourth Medical Service, February 2, 1933, with a condition of hemiplegia that had developed suddenly the same day. She could not talk and at first was unconscious. Later in the evening she seemed to understand events around her. Her heart was enlarged and there were systolic and diastolic murmurs. The pulses were regular except for occasional extrasystoles. Thirteen days after admission it was found that the left leg was cold and cyanotic. There was no history obtainable as to the duration of this condition. She was found to have

no pulsations in the leg and it was blotchy and was apparently developing a dry gangrene. She was transferred to the Fifth Surgical Service on February 13.

At operation the femoral artery was exposed and found to be contracted to a diameter of 0.5 cm. and pulseless. Its wall was quite injected. It was opened and found to contain a secondary clot. A large amount of clots were removed from above by means of a vein stripper, but only a poor flow of blood resulted. The intima was seen to be so damaged by the duration of the embolus that no further procedure was carried out. The wound was closed. Five days later a midthigh amputation was performed. She died 18 hours postoperative.

Case 24.—F. S., female. Admitted to the Fourth Medical Service, February 13, 1933, presenting a typical picture of acute cardiac decompensation with hypertension, arteriosclerotic heart disease and auricular fibrillation. She was responding well to rest and treatment when, on March 17, at 9:00 A.M., she noticed a sudden severe pain in the left leg. This was followed by paresthesia and anesthesia. It became cold to touch and no pulse could be found below Poupart's ligament. Examination also just before operation showed râles at both bases.

At operation the left femoral artery was exposed and no pulsation found. It was opened and the vein stripper was passed upward, which effected the dislodgment of some fragments of clot. On the fourth instrumentation, this time with a block tin gallbladder scoop, the main clot was evacuated. Wound in artery sutured. Popliteal artery exposed and found not to pulsate. Returning to femoral, a new clot was found at the suture line. This was removed through a new distal incision. This incision and the two wounds were then closed.

Three days later the circulation in the left leg was apparently adequate and her general condition was good. On the fifth day she developed a cerebral embolus, which resulted in a right-sided paresis and aphasia, but there was good circulation in the leg. Five weeks later the circulation and strength had returned to the left leg although the pulses never returned in the popliteal space, the ankle or the foot. The paralysis also disappeared. She was discharged to the Medical Out Patient Department.

Case 25.—M. C., female, age 72. Admitted March 3, 1933, to the Fourth Medical Service, in a condition of marked decompensation and with edema of the legs. There was an irregular heart from many extrasystoles. On the ninth day after digitalization and salyrgan diuresis, the legs were found to be cold and purplish. No popliteal or lower pulses were found on either side. Any surgical procedure was considered too hazardous. She died three days later.

Autopsy.—Old coronary occlusion. Areas of milky white thickened epicardium. Examination of the legs and arteries was unfortunately overlooked.

Case 26.—P. R., male, age 46. Admitted April 1, 1933, to the Fourth Medical Service, subsequent to a cerebral accident. No previous history was obtained. The heart was fibrillating. His extremities were not abnormal on admission. His heart failure increased after admission and later both legs became cyanotic. The popliteal pulses were found to be absent. Later both legs became mottled. He died, April 4, 1933.

Autopsy.—Mural thrombi in the left ventricle and an old infarct of the ventricle. Lower, middle branch of left descending branch of the coronary artery was occluded for 2 cm. A large thrombus occluded the lower part of the abdominal aorta.

Case 27.—M. G., female, age 50. Admitted May 26, 1933, to the Fifth Surgical Service. Five hours before admission she was awakened by a sudden severe pain in the right leg and foot. This was followed by numbness and tingling. Previously the patient had been treated for diabetes and "heart trouble" at many clinics. After three hours she was seen by her physician, who sent her to the hospital. Examination showed a sick looking uncoöperative patient. Râles were heard at both bases. The apex beat was neither seen nor felt. There was enlargement to the left almost to the axillary line. The sounds were completely irregular and there were no murmurs. The radial vessels were tortuous and beaded. The liver edge was three fingers below

the costal margin. No femoral or any lower pulsation could be felt on the right. On the left the femoral pulse was felt, but it was weak and the lower ones were absent. There was marked duskiness below the middle of the right thigh with pallor of the leg and foot. The left leg was warmer than the right one.

Operation.—Right upper femoral incision. Artery exposed above profunda branch. It was empty and nonpulsating. It was freed and catheters were passed around it. It was opened and there was no bleeding. A small vein stripper was passed to the aorta and on withdrawing it a large amount of mushy clot came out followed by free bleeding. Wound closed, incision over popliteal artery showed good pulsation, but one over the dorsalis pedis showed none. The wounds closed in layers. The next day both legs became markedly cyanotic and in the afternoon she died with symptoms suggesting cardiac failure.

Case 28.—M. S., female, age 85. Admitted May 31, 1933, to the Fourth Medical Service, in a comatose condition, and no history was obtained. She was fibrillating, and both extremities showed popliteal pulses and dorsalis pedis to be present, but weak. The next morning the intern noticed that the left lower leg was cold and that the popliteal and lower pulses in this leg were absent. There was no way of learning exactly when the circulation became impaired. Further examination showed a pulse of 136, and a completely irregular rhythm with a deficit of 50 beats. The left border of the heart was in the axillary line and there were râles at the bases.

Operation.—Upper femoral artery exposed for two inches. It had no pulsation. It was controlled with catheters and opened. Vein strippers were passed and soft mushy clots dislodged followed by a good flow of blood. The dorsalis pedis was then exposed, but no circulation found in it. Popliteal exposed and found to be beating weakly. The wounds were closed. Patient died 12 hours later of heart failure.

Autopsy.—The body was that of a small emaciated woman. There was hypertrophy of the left ventrical and marked dilatation of the right auricle. Myocardium of the left ventricular apex was practically replaced by a fibrous tissue wall 2 Mm. thick, which bulged to form slight dilatation of the chamber. The endocardium of this region was white and opaque. The middle portion of the posterolateral wall of the left ventricle for an area approximately 4 cm. square near the base was dark-brownish red, and softened. The valves were negative except for slight arteriosclerosis of the aortic cusps and the anterior mitral curtain. The endocardium over an area approximately 2½ cm. square on the posterior wall of the left auricle was slightly roughened and covered by fibrin. In addition a flattened partly organized thrombus 2½x2x½ cm. was adherent along one edge. The coronaries were tortuous and both right and left vessels pipe-stem in character. However, no complete closure or embolus was found in them. The left femoral artery was exposed at the site of the operation. It was of pipe-stem character and was not opened.

Case 29.—L. C., female, age 47. Admitted June 1, 1933, to the Sixth Surgical Service. One week ago she had had a sudden pain in the left leg. The pain has increased steadily. The heart was fibrillating and there was gangrene of the leg to the knee. Amputation was performed the next day and she died one day following it.

Case 30.—J. C., male, age 75. August 2, 1933, admitted to the Fifth Medical Service, but immediately transferred to the Fourth Surgical Service. Intermittent claudication had been present for five years. He had suffered an acute, severe pain in the left leg 48 hours before admission. On examination the leg was cold, numb and cyanotic below the knee. There was a faint line of demarcation. No popliteal or femoral pulse. His heart was regular. Amputation was performed two days later. He died of gas bacillus infection three weeks after operation.

Case 31.—A. F. E., male, age 40. Admitted August 31, 1933, to the Third Medical Service. Six days previously patient had had a sudden pain in the right arm followed by coldness and blueness of the hand. These had cleared without treatment, but the hand was very weak. On examination there was evidence of mitral stenosis

with fibrillation and absent pulse and blood pressure in the right arm. After ten days in the hospital he was discharged.

He was readmitted, October 24, 1933, to the same service for another attack of heart failure. In the intervening four weeks previous to the second admission, he had had the same kind of experience with the left arm. This had also cleared, leaving absent pulses on this side too.

He was admitted to the Fifth Medical Service on May 20, 1934, moribund, with alcoholism and pneumonia, and died in 24 hours. The case was considered medicolegal, but there was no autopsy.

Case 32.—B. H., female, age 64. Admitted October 31, 1933, to the Fourth Surgical Service, after having had a sudden severe pain in the right leg 48 hours before, which had remained and increased in severity. The leg had become white and later blue. On examination the foot and leg were cold and cyanotic. The popliteal pulse was not felt, but the femoral one was. There was no note of the heart or pulse. She was treated with dry heat for eight days. She became irrational during this time. On the eighth day the leg was amputated. She died two days later.

Case 33.—M. S., female, age 80. Admitted November 15, 1933, to the Fourth Medical Service. She came in on account of precordial pain and was found to have arteriosclerotic heart disease with auricular fibrillation and decompensation. Roentgenologic examination showed fluid at both bases, some atelectasis, enlargement of the heart and calcification of the aorta. She improved slowly and slightly on medication with digitalis. She was, however, still in the hospital two months later, on January 15, 1934, when she had a sudden severe pain in the right leg. This persisted for two hours before she was transferred to the Fifth Surgical Service. Examination then showed a senile woman, acutely ill and in great pain. She was slightly dyspneic and cyanotic. There were râles at both bases and the heart was enlarged and its beats slow, but totally irregular. The sounds were of fair quality and there were systolic murmurs. The right lower leg was pale with areas of bluish discoloration beginning about six inches below Poupart's ligament. It was cold. Femoral pulses could be felt on both sides, but below this level there were palpable pulses only on the left.

Operation.—The femoral artery was exposed at the point of disappearance of its pulsation. A clot could be felt in the vessel and slight end thrust pulsations could be seen. Catheters were passed. The artery was opened over the clot, which was squeezed out. There was an excellent flow of blood. The incision was closed with a single continuous suture. The dorsalis pedis and popliteal pulses became immediately palpable without cutting down to expose them. The wound was closed in layers.

The postoperative course was uneventful except that later the dorsalis pedis pulse disappeared again, without, however, in any way disturbing the nutrition of the foot. The other foot and leg pulses remained palpable. She was discharged, walking well, on February 1, 1934.

Case 34.—J. K., male, age 52. Admitted December 22, 1933, to the Fifth Medical Service. For three weeks the patient had suffered from generalized aches and pains, and for one week night sweats. For one day there had been chills and vomiting. He had had rheumatic fever in childhood. He was not fibrillating. His course in the hospital was typical of subacute bacterial endocarditis. Laboratory work confirmed this diagnosis. Streptococcus viridans was shown on repeated blood cultures. Two weeks after admission he noticed pain in the left knee and numbness and coldness of the leg. No pulse could be felt in any artery in this leg. However, he was given no treatment and no gangrene developed. He died January 31, 1934.

Case 35.—P. S., male, age 84. Admitted to the Fourth Medical Service, February 15, 1934, complaining of difficulty in talking, which had come on the day before. There was no paralysis and he was apparently conscious and rational. On examination he showed dulness and râles at both bases. His heart was not enlarged and was regular in rhythm except for a few extrasystoles. The peripheral vessels were thickened and

tortuous. While being observed on the Medical Service, he was disoriented at times and showed no return of the ability to speak. On the sixteenth day his right foot suddenly became blue and cold and no pulsation could be felt in either dorsalis pedis. Both popliteal pulses were also absent, but the femorals were present, stronger, however, on the left. He was transferred at once to the Fifth Surgical Service.

Operation was performed four hours after the onset of pain. An incision was made in the femoral artery and the clot was removed. Good back bleeding was demonstrated and the wound closed. The leg became gangrenous. The lower leg was amputated two months later and the thigh amputated five weeks after the leg. He was discharged with a good stump two months after the second amputation.

Case 36.—F. W., male, age 83. February 24, 1934, admitted to the Fifth Surgical Service. He had been bedridden three months, failing mentally. Treatment had been given for heart failure. One week ago he got out of bed and fell down. Since then progressive discoloration of left foot and leg had developed. Examination showed that the heart was inaudible. Pulses were felt in the groin, irregular, but not fibrillating. There was no popliteal pulse. He was moribund and died three hours after admission.

Case 37.—E. D., male, age 54. March 3, 1934, admitted to the Fifth Medical Service. He had suffered for many years from heart disease. Two days before admission he had a sudden numbness and coldness of the lower part of the right leg. He was not fibrillating. Pulses in this leg were absent. No operation was advised because of his poor condition. No gangrene was present and it was thought not to be necessarily impending. The leg did well, but on the tenth hospital day he had sudden severe abdominal pain, nausea and vomiting, and died in 30 hours. A diagnosis of mesenteric thrombosis was made. There was no operation or autopsy.

Case 38.—S. W., male, age 57. Admitted April 5, 1934, to the Fourth Medical Service. He had suffered from dyspnea for 15 years. Three years ago he had a left hemiplegia and two subsequent "shocks" two and one years ago had also occurred. Three days before entry he had a severe pain in the right forearm followed by weakness and numbness. Examination showed fibrillation and absent radial and brachial pulses on the right. Cyanosis of the right hand, but no gangrene. Operative intervention was not thought indicated because of the duration and the obvious adequate collateral circulation. Hand subsequently did well. He was digitalized. On the sixth day he had a sudden pain in the left leg with other signs of embolism. Operation was again thought inadvisable owing to his being such a poor risk. He died 15 days later. No amputation was performed.

Autopsy showed at the apex of the left auricle an attached thrombus with white thick endocardium under it. Thrombosis of aorta was present from the renal artery down, with gangrene of both legs. There was also embolism of the interior mesenteric artery with gangrene of the intestine supplied by it.

Case 39.—G. B., male, age 67. Admitted April 6, 1934, to the Second Surgical Service. This record is so incomplete as to be of no value. The patient came in moribund and died in four hours. He had had a cerebral accident. Pulses were absent in the right arm, which was swollen and blue.

Case 40.—P. W., male, age 50. Admitted June 28, 1934, to the Second Medical Service and transferred at once to the Fifth Surgical Service. He had had cramps in both legs for five weeks. Five hours before entry there was a sudden severe pain below the right knee followed by numbness and coldness of the leg. He was not fibrillating. There was no pulse below the upper femoral on the right. Pulses were normal on the left. Embolectomy of the right femoral was performed at once. Incision was made over the clot and it was removed. The wound was sutured and the circulation in the leg was immediately reëstablished. He was discharged two weeks later, walking and with adequate circulation in the leg. He was readmitted to the Fifth Surgical Service August 3, 1934. Four hours before he had had another attack of the same type of pain and the same other symptoms in the same leg. They were, however, slightly milder.

Operation was performed at once. Incision was made along the old scar. The artery was found to be pulsating normally to the point of the previous incision in it. At this point there was dense scar tissue. The scar was opened. The artery was found to be completely closed by scar. A clot was removed, but the artery was so scarred that it was found to be impossible to reëstablish circulation through it. It was therefore sectioned and ligated. He recovered with the leg well again. No pulsations could be felt below the ligation. He was transferred to the Fourth Medical Service for treatment of the heart. He did well and was discharged against advice. His final medical diagnosis was asthma rather than heart disease.

Case 41.—C. X., male, age 70. Admitted June 28, 1934, to the First Medical Service, suffering from dyspnea and edema, for which he had also been treated on the same service four months before. Râles were found at the bases and there was fibrillation of the heart. On July 9, he had a suden hemiplegia and also pain in the left foot, which rapidly became cold. There was no popliteal pulse, but a good femoral one in this leg. On account of the hemiplegia and very poor condition, operation was not advised. On July 18, he was seen again and amputation was still not advised. He then gradually became weaker and died August 6, 1934.

Autopsy showed gangrene of the leg to the midtibia. The heart was negative except for moderate coronary sclerosis and a patent foramen ovale. There was marked sclerosis of the aorta. The left common iliac was almost occluded by an old thrombus. The femoral at midthigh was full of old adherent clot. The source of the embolus could not be determined.

Case 42.—M. L. L., female, age 26. September 6, 1934, admitted to the Third Medical Service. The patient was eight months pregnant and had had cough, dyspnea and edema of the ankles for two months. There had been pain in the left shoulder and arm for two days. The heart was regular. She had had a hemiplegia three years before. In the examination of the left arm nothing was noted about its color or temperature, but the pulse was absent at all points and the blood pressure was also absent. She went into labor September 7, and was delivered by cesarian section. She had had a previous one. The notes are incomplete, but apparently no gangrene developed in the arm. She died seven days later.

Autopsy.—There was no note of the arteries. The heart showed gray-white fungoid masses 2 to 3 Mm. long and 1 to 2 Mm. in diameter on the mitral and aortic valves. The rest of the heart was negative and it was of normal size. The pathologist's diagnosis was acute bacterial endocarditis. She also had an organized hemorrhage of the internal capsule of the brain.

Case 43.—W. R., male, age 49. Admitted December 31, 1934, to the First Medical Service, with bronchopneumonia, heart failure, and fibrillation. One week later he suddenly became cyanotic, irrational and restless and the pulse disappeared from the left arm below the axillary artery. He died the next day. There was note of the nutrition of the arm.

Case 44.—M. B., female, age 67. Admitted February 24, 1935, to the Fourth Medical Service, suffering from extreme dyspnea of three months' duration. She had had a period of unconsciousness on the day of entry. She was not fibrillating, but had many extrasystoles. On the fifth day a cramp on the left leg continued all night. On examination in the morning the leg was found to be cold, cyanotic, and pulseless. Expectant treatment was advised. The leg seemed to be in good condition for several days, but after the eighth day two toes became black and infection started up the leg. On March 21, amputation of the thigh was performed. She survived and was discharged well.

Case 45.—I. C., female, age 44. Admitted to the Fourth Medical Service on March 20, 1935. She had had rheumatic heart disease. A diagnosis of cerebral embolus had been made in 1928. Increased dyspnea and decompensation had developed since then. Five days before admission there was a sudden weakness of the left face and

right arm and she was mentally confused. Twelve hours before admission she had a sudden severe pain in the right leg, which became cold and hard. Examination showed fibrillation and absent popliteal and lower pulses on the right side. Operation was not advised as collateral circulation was adequate. Treatment by Buerger's exercises. She has had two subsequent admissions for cardiac decompensation. Her legs have remained in good condition.

Case 46.—R. M. H., female, age 48. Admitted April 17, 1935, to the Aural Service, for acute mastoiditis. There had been a discharge from the ear for five weeks. She also had diabetes. A simple mastoid operation was performed with exposure of the lateral sinus in which no thrombosis was found. On the third day the right radial pulse disappeared. There was no note made of higher pulses. The hand became cold and clammy with areas of ecchymosis on the outer half. No treatment was given for this and no further notes were made concerning the hand. She died on the fifth day after the operation.

Autopsy.—There was no description of the arm, cellulitis of the neck and scalp, healed mitral endocarditis. There was also cardiac infarction with a mural thrombus.

Case 47.—P. L., male, age 60. Admitted June 11, 1935, to the Fifth Surgical Service, suffering from pain in the right arm of five hours' duration. He was a chronic alcoholic and had been drinking heavily for two or three days. He had pain in the left leg, but no change in color of the leg and could walk well. The arm became cold, pale and numb. The right radial and brachial pulses were absent, but the axillary was felt. Embolectomy was performed on the upper brachial. A large clot was removed and there was free back bleeding. The radial pulse returned. Discharged, well, July 27, 1935.

Case 48.—A. R., female, age 63. Admitted June 21, 1935, to the Fifth Surgical Service. At 4:00 P.M. she had a sudden pain in the right leg below the middle. In one-half hour the leg became pale and cold. She arrived at the hospital seven hours later. She was fibrillating. A femoral pulse was felt, but lower ones could not be felt. Embolectomy with probing dislodged the clot from the femoral artery. There was good back bleeding. Wound healed well and the circulation became adequate. She was discharged well on July 15. She was readmitted to the First Medical Service, November 28, 1935, on account of increased dyspnea. She was hospitalized three weeks, was digitalized, and discharged improved, December 14, 1935.

Case 49.—M. M., female, age 35. Admitted July 16, 1935, to the First Medical Service, suffering from dyspnea and edema. She was fibrillating and was therefore digitalized. Six days later it was noted that both legs were mottled, bluish and painful. The left femoral pulse was absent and the right one was weak. Both legs were treated by a Collins' "Vasculator." The left improved, but the right did not. July 29, 1935.—Amputation of the right leg. She was discharged six months later.

Case 50.—W. M., male, age 75. Admitted July 20, 1935, to the Second Medical Service. He came in unable to speak on account of hemiplegia, but not comatose. No competent history was obtained. He was not fibrillating, but had extrasystoles. The left leg was colder than the right and had a "greenish pallor." The dorsalis pedis and popliteal arteries were not felt. The left femoral was weaker than the right. The leg gradually became blotchy and the left femoral pulse disappeared. He died on the second day.

Case 51.—C. G., female, age 62. Admitted August 8, 1935, to the Third Medical Service, in coma. She had had kidney trouble and high blood pressure. The whole right side of the body was paralyzed. Pulse was regular. Twenty-four hours after admission it was noticed that the right leg was cold and cyanotic. No pulsation could be found in it. She was treated by papaverine, heat and codein. She died 24 hours later.

Case 52.—S. G., male, age 32. Admitted August 10, 1935, to the Fifth Medical Service. He had been previously in the hospital three times since October 15, 1934, for decompensation of the heart. He had mitral disease with fibrillation. Two hours be-

fore the present admission he experienced a sudden severe pain, numbness and coldness of the left leg. Examination showed the leg blue from just above the knee down. No pulse was found below the femoral in this leg. Embolectomy at the junction of the profunda branch. A large clot was removed. After 30 minutes there was no return of circulation to the lower leg. The popliteal artery was therefore opened and an old thrombosis demonstrated. Treatment with the "Vasculator" was started at once and at first this treatment improved the circulation a great deal. The skin, however, became abraded in the thigh by the machine, so that it had to be stopped after 24 hours. The leg rapidly became gangrenous and amputation was performed four days later. His wound broke down, but eventually he was discharged.

Case 53.—C. R., female, age 64. Admitted September 9, 1935, to the Fifth Surgical Service. Twenty-four hours before she had had a sudden pain in the left leg. Examination showed fibrillation. The leg was of purple color below the knee. Femoral and lower pulses were absent. Three days later thigh amputation was performed. Three weeks later she was discharged.

Case 54.—M. DeS., female, age 72. Admitted September 30, 1935, to the Fourth Medical Service, suffering from dyspnea, cough, and edema. She was fibrillating. She improved on treatment and her heart became regular on October 22. Later the same day, absent pulse in the right radial and brachial anterior was noted. Numbness and cyanosis of this hand developed.

Embolectomy of the brachial artery was performed. A clot was found and removed and good flow of blood established. Damage was done to the intima, which seemed to be rolled up so that it came out with the clot. Circulation was not established after operation, but no gangrene developed. November 19, 1935.—Discharged with a good arm.

Case 55.—D. McN. male, age 82. Admitted November 4, 1935, to the Fourth Medical Service. He was irrational, dehydrated, dyspneic and fibrillating on admission. He did not respond to treatment. On November 19, parotitis and bronchopneumonia were noted. On November 22, the right leg became purple, cold, pulseless. He died the same day.

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DISCUSSION.—DR. HARRY H. KERR (Washington, D. C.): The problem of handling an arterial embolus is one that we should all be prepared for because of its suddenness. As Doctor Lund says, it most commonly occurs in cases of fibrillating hearts that sometimes throw off large emboli.

My experience in one case is worth reporting, because it suggests a simplified method of operation. I had a case of so called saddle thrombus of the bifurcation of the aorta, really an enormous embolus from a fibrillating heart. I saw the case early enough to operate, tape the aorta and common iliacs, open the left common iliac transversely, and remove the recent clot, which was friable and had to be removed piecemeal. I was afraid to put a curet into the artery for fear of spilling it over into the opposite side, and, therefore, resorted to suction. The man did remarkably well. He regained pulsation in his peripheral vessels, and I was quite proud of the result. On the eighth postoperative day, however, another embolus straddled the bifurcation of the aorta, and all his previous symptoms recurred.

Being a little fearful of performing another major abdominal section on the case, I resorted to suction from below under local anesthesia. The left femoral artery was opened in Scarpa's triangle, and a well oiled soft rubber catheter, attached to the suction apparatus, was passed up the artery 1 cm. at a time, and withdrawn after each advance. In these cases that are sometimes desperately ill, a relatively minor operation can replace the more formidable abdominal section.

I have had the opportunity of testing this procedure on one case since. The arm was involved, and perhaps should not have been operated upon, but with the chance of testing this therapeutic measure, I removed an embolus from the axillary artery with suction from below. Another case of saddle thrombus had been operated upon by this method at my suggestion by another surgeon, but unsuccessfully.

DR. ALBERT O. SINGLETON (Galveston, Texas): Doctor Lund in his paper did not discuss technic, but Doctor Kerr has started the technical discussion, and I wish to mention some experiences which I have had with an upper arm embolus at the bifurcation of the brachial artery. The artery was opened, the proximal circulation was found free and some clot forced from above through the opening. The clot below the obstruction was squeezed out by massaging the arm upward from the outside, and then the opening in the artery closed. To our disappointment, the hand remained blanched and no radial pulse resulted. We immediately opened the artery a second time and found that another clot had formed, which was again evacuated by massage of the artery from the outside. Then the radial artery was exposed at the wrist, a small needle was passed through the wall into the lumen, and sodium citrate solution forced into the artery. The sodium citrate solution returned through the wound in the brachial, removing other small clots; and during the suturing of the opening in the artery, the citrate solution was allowed to run through, preventing further clotting. Following closure of the artery, the radial pulse was present, and the arm and hand circulation remained normal.

When a thrombus remains in an artery for a few hours, the reaction from the intima tends to cause reformation of the clot quite promptly with slowing of the blood stream; therefore, the citrate solution in the artery tends to prevent clotting until the circulation is turned through. According to Doctor Lund, obstruction to the first part of the brachial does not result in gangrene. This is an interesting point, and quite opposed to the prevailing opinion. We have seen a gangrenous hand in an old man following an embolus at this level.

Dr. Edwin Beer (New York): Having had experience with three or four saddle thrombus cases, I think it might be informative to put them on record.

The first patient was operated upon rather late, after the saddle thrombus developed, by the transabdominal route; a fatality resulted. The common iliac was opened, just as in Doctor Kerr's case, and the clot readily extracted. Two subsequent patients were operated upon, under local anesthesia, through the femoral artery. No difficulty was experienced in passing a rubber catheter, well lubricated with Vaseline, into the common iliac with aspiration of large clots. One case came to autopsy and showed how impossible it would have been to cure the case or clear out the artery, because the thrombus ran all the way up to the diaphragm, covering both renal arteries. The other case resulted fatally but did not come to autospy.

The fourth case was almost identical with the three cases previously cited, and we were about to operate, but owing to hesitation on the part of the patient, as the operation was to be performed under local anesthesia, nothing was done, and strange to say, the man got over his serious accident, possibly only a right common iliac artery block, with a loss of only the big toe.

Following this experience, I wrote Dr. Einar Key, in Stockholm, to get information as to how he decides, and when he decides, to operate upon the saddle thrombi and emboli in the common iliac artery, and I must say the information obtained from him was very unsatisfactory and not at all informative.

Dr. I. A. Bigger (Richmond, Va.): I have seen two patients with saddle emboli at the bifurcation of the aorta. One of them was so far advanced it was thought unwise to attempt anything, as the patient had a beginning gangrene of both feet and lower legs.

The other patient was seen about 15 hours after the embolism had occurred and there was already some discoloration of the feet and lower legs. In spite of this, it was thought that something might be accomplished by removal of the embolus, and operation was advised. The abdomen was entered through a low midline incision under local anesthesia. We had planned to make an incision in the lower portion of the aorta, with the hope that the entire embolus could be removed from both iliac vessels by this approach. Unfortunately, we found that the wall of the aorta was extensively calcified, and that there was considerable calcification of the wall of the left iliac artery. The right common iliac artery showed very little calcium deposit, so an incision was made through the wall of the lower portion of this vessel and an attempt made to remove the embolus by milking it out from above. This was unsatisfactory because of extensive calcification in the vessels, so it was finally removed by suction.

When a good flow of blood had been obtained, the opening in the vessel wall was closed by sutures, but at about the time the closure had been com-

pleted, the pulsations became less distinct and finally ceased. It was thought that a thrombus had formed, probably as a result of injury to the intima of the vessel while the attempt was being made to milk the embolus out.

I should like to ask Doctor Lund if he knows of any case in which a saddle thrombus has been removed through the wall of the aorta, and, if this has not been done, would it not be the logical approach?

DR. CHARLES C. LUND (Boston) closing: I am very much interested to hear of these saddle embolus cases and the way they were handled. In my group, there were two instances of bilateral thrombi. I do not know whether the emboli extended right up to the bifurcation or not. I doubt if they did, because it did not seem that enough clot was recovered to have had it extend as far as the femoral openings.

I have had a feeling, all the way along, that I would much rather operate upon one of these emboli at a point below than at a point above the clot. You have the blood pressure tending to push the clot down, and either with suction or with an old fashioned vein stripper, with a bulb on the end of a wire, you can break it up and the blood pressure will push the fragments out.

The bilateral cases were both approached through the femoral artery. One of them was entirely successful; the other was a failure, but it was one of my earliest cases and was undoubtedly of too long duration.

I am afraid I do not recall all references in the literature and, therefore, cannot answer Doctor Bigger's question categorically; but many incisions have been made through the aorta by surgeons to relieve this condition, and I recall one definitely by Doctor Walker, in 1925. Other incisions have been made very close to the aorta, in either one or the other iliac arteries, and successful removals of saddle emboli accomplished. I have found most of these patients in pretty desperate condition, and have, therefore, deliberately avoided the abdominal approach, although I admit that it has been frequently, and successfully, employed. I think Doctor Beer has had a lot of bad luck with his patients.

There is one other thing that I would like to mention, that I neglected to include in my paper. What happens to these patients after they leave the hospital? Is it worth while attempting these operations at all, or are their hearts so bad that they are going to die right away? I know most of my end-results, but I do not know quite enough to tabulate them as yet.

In the articles on this subject by Swedish authors, which are recent, especially one concerning the whole Swedish experience, it is shown that from the time the patient gets out of the hospital, one-quarter of them die in the first year, one-half will die in the first three years; at the end of five years, one-third will be alive, and at the end of ten years, one-eighth will still be living. If you plot that in a curve, it is practically identical with that which was recently published from the Pondville and Huntington Memorial Hospitals on the results of treated cancer of the breast. That does not mean all operable cases, but all cases that had important roentgenotherapy or operation. The curves seem to appear exactly superimposed. Therefore, I think the remote results are good enough to warrant this kind of operative procedure, provided one considers that the remote results of operations and other treatment for cancer of the breast are worth while.

STUDIES IN THE ETIOLOGY OF ACUTE APPENDICITIS*

THE SIGNIFICANCE OF THE STRUCTURE AND FUNCTION OF THE VERMIFORM APPENDIX IN THE GENESIS OF APPENDICITIS

A PRELIMINARY REPORT

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THE observations of the nineteenth century stressed mechanical causes as responsible agents in the genesis of inflammations of the vermiform appendix. Convincing evidence and substantial proof, however, were lacking to establish mechanical causes as the chief etiologic agency of appendiceal suppurations. Speculation and armchair philosophizing created a considerable literature of "paper experimentation" concerning the origins of this disease in which complete sight was lost of the pathologic observations of our medical ancestors and new factors of latitude, longitude, diet and habits of life came to occupy, in the medical mind, a significant rôle in the causation of the disease. The confusion over admixture of fact and speculation has grown until what is speculation and what is fact is scarcely longer discernible.

The cogency of the vigorous declarations of Professor Aschoff, who has come to believe that acute suppurative appendicitis is essentially a specific bacterial disease (not unlike gonorrhea in its specificity) due to the enterococcus Type B (Gundel), has won many converts for the idea that appendicitis is infectious in origin.

The significance of the observations made by Volz, Matterstock and Fitz with reference to the obstructive factor, however, cannot be lightly dismissed or set aside. The surgeon, conscious of the paucity of specific infections in the alimentary canal and its appendages and impressed with the unfavorable anatomic arrangement for satisfactory function presented by the long narrow diverticular-like vermiform appendix, does not readily abandon the notion that obstruction is an important item in originating the disease.

Purpose of the Present Study.—This study was undertaken with the consideration of investigating the minute anatomy of the vermiform appendix of man, to determine whether the obstructive features of acute suppurative appendicitis found an accordant explanation in the behavior of this appendage. In a previous study many of the numerous theories and hypotheses relating to the origins of appendicitis were discussed at length. An attempt was also made to evaluate the likely significance of the factors of infection and obstruction. It was pointed out also that in the severe forms of the disease in man (perforative and gangrenous appendicitis) a demonstrable obstruction, often

* Supported by a grant from the Research Fund of the Graduate School.

a fecalith, was usually present. Subsequently the presence of a mechanism exhibiting resistance to outflow from the lumen of the vermiform appendix and interfering with satisfactory evacuation of its content was described.[26] This latter finding suggested the necessity of a more extended exploration of the anatomic and functional features of the vermiform appendix.

Plan of This Study.—(I) It is proposed first to examine the nature of the appendicocecal union in man and to note: (1) The manner in which the appendix meets the cecum; (2) the nature of the appendiceal orifice; (3) the presence of mucosal folds overlying the orifice and their nature; and finally (4) the disposition of the muscle fibers at the site of appendicocecal union.

(II) It is proposed further to elucidate the nature of the resistance offered to intraluminal perfusion of the vermiform appendix by noting its order of magnitude in acute, interval and normal appendixes at the time of appendicectomy.

(III) (1) An opportunity to study this behavior of the appendix over longer intervals of time was afforded in sixteen patients with appendicostomies. Fifteen of these were made coincidentally during colostomy for malignant disease of the colon or rectum; the other was effected at the same time that a permanent ileostomy opening was made in a case with ulcerative colitis.

(2) The appendicostomy opening was cannulated to determine whether fluid was secreted by the appendix.

(3) The effect of various drugs upon the resistance to luminal outflow was also determined in several instances.

(4) In a few others, organisms obtained from the exudate of acute suppurative appendicitis were transferred to the lumen of appendicostomy openings.

(5) In others a lead birdshot No. 9 (one-ninth inch or 2.79 Mm. in diameter) was inserted into the lumen of the appendicostomy.

(6) In a few instances in which the exteriorized portion of the appendix was long, segments were cut off and studied histologically after the maintenance of increased intraluminal pressure for several hours.

(IV) In the excised appendix after appendicectomy, the resistance to luminal outflow was again noted; in addition, by suspending segments of the appendix in an oxygenated and temperature controlled water bath attached to a muscle lever, the contractions of both the circular and longitudinal muscle coats of the appendix could be studied. The effects of certain drugs upon the activity of the appendix were better studied in this medium than in patients with appendicostomies.

(V) The retention of foreign material by the appendix has been further studied by spectrographic studies upon the intraluminal content of the appendix in patients who had previously ingested barium.

(VI) The results noted in the above experiments (Group III, item 2) suggested the necessity for investigating whether fluid was secreted or absorbed in the cecal appendages of other animals.

(VII) Determination of the volume of the lumen of the vermiform

appendix of man has been made to ascertain what intraluminal increase in volumetric content and tension may occur without perforation.

This broad study of the problem of appendicitis cannot be related in detail in this paper. Several additional expositions will be necessary to recount all the evidence with a bearing upon the problem which has been gleaned from the study. It is proposed only to state briefly here what has been done and what the results are.

I. The Nature of the Appendicocecal Union.—*The Material:* Through the cordial coöperation of the Department of Pathology of the University of Minnesota, an ample postmortem material was obtained.* Over 800 specimens of the human proximal colon, including the cecum, vermiform appendix, and terminal ileum, became available to us. Many of these specimens were received in the fresh state, one to 24 hours after death. The usual mode of dealing with these specimens was to fill the lumen of the specimen with 4 per cent formalin solution (both ends of the gut being tied). It was then placed in a tank containing similar fluid. This method of fixation, it was felt, eliminated contraction phenomena to some extent. Specimens which had been injured or exhibited unusual contraction were excluded from the study. In a number of instances, the specimen was filled with gelatin in the fluid state to show the internal topography of the ileocecal valve, the cecal pouch and the appendicocecal union. Casts of the appendix and cecum were made also in a number of instances by filling the preparation with melted Wood's metal. A few air dried specimens were also studied.

(1) *How the Appendix Meets the Cecum.*—In 1885, in his Hunterian Lectures, Treves studied the external form of the appendicocecal union and established four general types. Berry and Jacobshagen have employed the grouping of Treves. The Type I cecum of Treves is the smooth embryonic funnel shaped organ with the appendix at the apex and true center of the most distal portion of the cecum. The Type II cecum is similar to Type I except that the cecum is sacculated evenly on both sides and there is not, as in Type I, a gradual fusion of the lumina of appendix and cecum, but on the contrary, a sudden transition from the one into the other. Type III shows an increased sacculation of the lateral half of the cecum, thus forcing the site of appendicocecal union far mesiad to the left toward the ileocecal valve and away from the apparent apex of the cecum. The Type IV cecum of Treves is characterized by an even greater lateral sacculation in which the medial wall of the cecum practically disappears and the base of the appendix in consequence comes to lie near the termination of the ileum. In this type, the appendixes are commonly adherent to the ileum.

A summary of our findings in a study of 262 cases is to be found in Table I. It is to be noted that all the fetal specimens fell in Group I. The majority of the specimens during the first year of life (from both term fetus

* The authors desire particularly to acknowledge the great assistance lent them by Dr. J. F. Noble, pathologist to Ancker Hospital, Saint Paul, and by Dr. N. F. Lufkin, pathologist to the Minneapolis General Hospital.

to the second year) fell also into Group I. In the older age groups (11 to 84 years), the majority fell into Group III.

TABLE I

CLASSIFICATION OF CECUMS

Age	Number	Treves' Type I	Treves' Type II	Treves' Type III	Treves' Type IV
Fetal	63	63	—	—	—
Term—1 yr.	25	20	—	5	—
1–10 yrs.	12	5	—	6	1
11–20 yrs.	7	1	—	5	1
21–30 yrs.	9	1	—	8	—
31–40 yrs.	16	1	1	13	1
41–50 yrs.	33	3	1	26	3
51–60 yrs.	37	7	1	27	2
61–70 yrs.	33	2	2	25	4
71–80 yrs.	23	2	—	18	3
81–84 yrs.	4	—	—	4	—
Total	262	105 (40.1)	5 (1.9)	137 (52.3)	15 (5.7)
Fetal	63	63 (100.0)			
Term—84 yrs.	199	42 (21.1)	5 (2.5)	137 (68.9)	15 (7.5)
Term—10 yrs.	37	25 (67.6)		11 (29.7)	1 (2.7)
11–84 yrs.	162	17 (10.5)	5 (3.1)	126 (77.8)	14 (8.6)
Treves	100	(2.0)	(3.0)	(90.0)	(5.0)
Berry	100	(10.0)	(6.0)	(80.0)	(4.0)

TABLE II

COMPARATIVE SIZE OF 477 APPENDICEAL ORIFICES

Description	Size (Mm.)	Number	Per Cent
Very Large	15 plus	2	0.4
Large	10–15	81	17.0
Medium Large	6–10	12	2.5
Medium	4– 6	155	32.6
Medium Small	2– 4	7	1.3
Small	0.5–2	210	44.1
Pin Point	0.5	10	2.1
Total		477	100.0

(2) *The Appendiceal Orifice.*—The interior of the cecum in the region of the appendiceal union was studied with the specimen in its usual anatomic position. That portion of the cecal wall including the superior margin of the vermiform process to the inferior lip of the ileocecal valve will be called the superior appendicocecal wall; the inferior portion of the cecum which continues with the inferior appendiceal wall will be designated as the inferior appendicocecal wall.

The appendiceal orifice varies considerably in size and shape as indicated in the accompanying tabulation of 477 orifices (Table II). In sixteen instances no appendiceal lumen could be demonstrated. These specimens will be studied subsequently in greater detail.

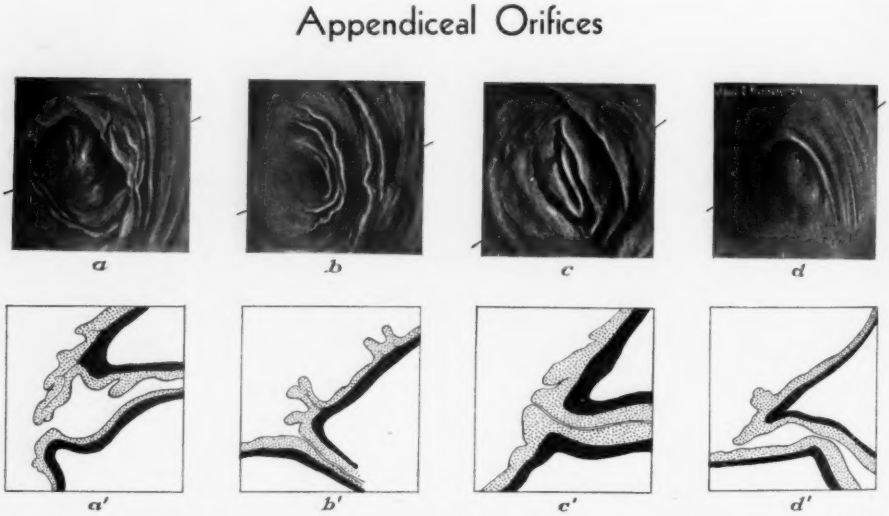

FIG. 1.—Drawings of some of the types of appendical orifices and mucosal folds observed; *a'*, *b'*, *c'*, and *d'* are sketches made from a section cut through the axis of the appendix as indicated by the short lines on the margin. (*a*) Very large round orifice with prominent Gerlach's mucosal fold overlying it (incidence in this series, 0.9 per cent). (*b*) Small crescent-shaped orifice with Gerlach's fold and secondary mucosal fold overlying the appendical opening (41.2 per cent). (*c*) Slit-like appendical orifice with Gerlach's fold and one large secondary mucosal fold (13.6 per cent). (*d*) Pinpoint orifice with persistent mucosal fold with Gerlach's fold overlying it (2.1 per cent).

In Table III the type of orifice has been classified as round, oval, irregular, crescent, and slit like. The size of the orifices has also been correlated and tabulated with its shape.

(3) *Mucosal Folds Overlying the Appendiceal Orifice.*—A mucosal fold overlying the appendiceal orifice was mentioned by Gerlach, in 1847, who described it as an inconstant semilunar fold of mucous membrane guarding the internal appendicocecal orifice. The careful German anatomist, Toldt, recognized this mucosal fold and it has come to be known as Gerlach's valve. Many, however, deny the existence of such a mucosal fold guarding the appendiceal orifice.

The presence or absence of folds about the appendiceal orifice was carefully noted in 526 specimens. If such folds are present, almost invariably they are to be found on the superior cecal wall. The primary fold overlying

TABLE III

COMPARATIVE SIZE AND SHAPE OF ORIFICES OF 477 ADULT APPENDICES

Size (Mm.)	Round Per Cent	Oval Per Cent	Irregular Per Cent	Crescent Per Cent	Slit Per Cent
15 plus	0.9	0.7	—	—	—
10–15	45.5	12.5	11.8	6.8	—
6–10	6.2	0.7	—	3.1	—
4– 6	16.1	36.8	41.2	44.3	24.6
2– 4	0.9	1.3	—	3.1	—
0.5–2	25.9	47.3	47.0	41.2	72.3
0.5	4.5	0.7	—	1.5	3.1
Total	100.0	100.0	100.0	100.0	100.0
Shape	23.5	31.8	3.6	27.5	13.6

the orifice has been described here as Gerlach's fold. A large number were subjected to microscopic examination to determine whether muscle fibers continued into the fold. With the exception of three fetal specimens, in which circular muscle definitely projected into the fold, muscle fibers were invariably

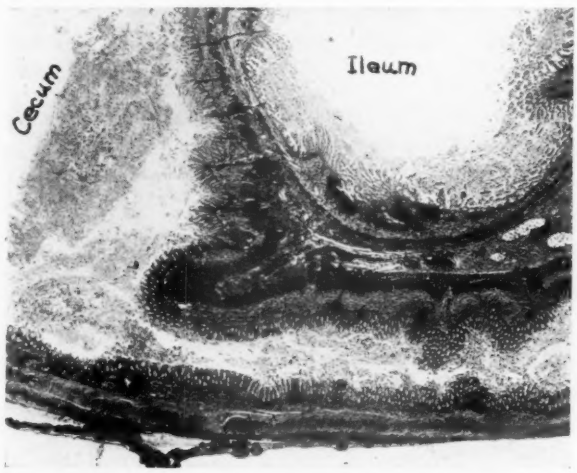

FIG. 2.—Gerlach's fold in a term fetus. There is definite evidence of muscle in the fo'd—an observation which apparently escaped notice heretofore. The presence of circular muscle in this fold has not been observed by us in the appendixes of adults. We would infer, therefore, that as the ileum and appendix increase in size that circular muscle disappears from Gerlach's mucosal fold.

absent (Fig. 2). In some instances, secondary mucosal folds were present on the superior cecal wall. These circular folds of mucous membrane form an inverted V over the orifice. They extend laterally for 1 to 2 cm. and fuse with the mucosa of the cecal wall. Folds lying at a distance greater than 2 cm. from the superior margin of the appendiceal orifice do not appear in Table IV. Gerlach's mucosal fold was noted in 81.5 per cent of 526 specimens.

TABLE IV

MUCOSAL FOLDS ABOUT THE APPENDICEAL ORIFICE *

Folds Present on Superior and Inferior Cecal Wall	Number of Specimens		Per Cent	
Gerlach's mucosal fold	183		34.8	
Gerlach's and one semilunar mucosal fold	147		27.9	
Gerlach's and two semilunar mucosal folds	82		15.6	
Gerlach's and three semilunar mucosal folds	1		.2	
Gerlach's and Nanninga's mucosal fold	16		3.0	
Total with Gerlach's mucosal folds		429		81.5
No folds about the orifice	89		16.9	
No Gerlach's fold; one secondary mucosal fold	1		.2	
Longitudinal mucosal folds	5		1.0	
Complete ring	2		.4	
Total without Gerlach's folds		97		18.5
Total orifices		526		100.0

* Mucosal folds about the appendiceal orifice of 526 adult and fetal cases, or 77.92 per cent of the total series of 675 specimens.

Table V indicates to what degree the appendiceal orifice was obscured by mucosal folds. It is to be noted that in the fifty-seven fetal specimens there was direct continuity between appendiceal lumen and cecal cavity.

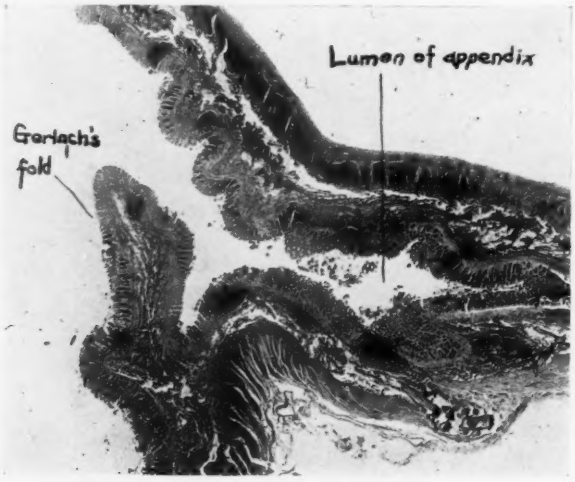

FIG. 3.—The more usual mucosal fold of Gerlach. Note the presence only of submucosa in it and the absence of muscle.

(4) *Disposition of Muscle Fibers at the Site of Appendicocecal Union.*—A study of the arrangement of muscle fibers where vermiform appendix and cecum merged was undertaken to determine whether a true sphincter of circu-

TABLE V

INCIDENCE OF OBSCURATION OF APPENDICEAL ORIFICES BY MUCOSAL FOLDS

	Hidden	Partially Hidden	Not Hidden	Total
Fetal	0	0	57 (100.0%)	57
Others	57 (12.3%)	77 (16.5%)	331 (71.2%)	465
Total	57 (10.9%)	77 (14.8%)	388 (74.3%)	522

lar muscle fibers was present. That such a circumstance might obtain was suggested in the occurrence of resistance to luminal outflow of fluid from the appendix. To this end, blocks about 1 cm. in length were cut including the tip of the cecum and the proximal portion of the appendix in 250 specimens. These blocks of the appendicocecal union were embedded in paraffin and cut—the larger number in the axis of the appendiceal lumen, a lesser number transversely. The former type of section was found to be more suitable for our purposes of studying the musculature. The majority of the sections were cut ten micra in thickness. Most of the sections were stained for microscopic study with hematoxylin and eosin and a lesser number with Mallory's azan-carmine stain. In many instances complete serial sections of the blocks were available for study.*

The results of this study will be reported in detail in a subsequent communication (Buirge and Wangensteen). It will suffice to say that no indication of a sphincter muscle at the site of union of appendix and cecum was observed. The more usual type of arrangement is indicated in Figs. 3 and 4. It was noted that thickening of the circular muscle in excess of that attending union of appendix and cecum occurred in 59 per cent of 250 specimens studied microscopically on the medial or ileal side of the appendicocecal union (Fig. 4). On the lateral side no such thickening was observed. The thickness of the combined muscle layer (both circular and longitudinal) was determined 1 Mm. beyond and proximal to the point of appendicocecal union in 74 of these specimens. A variable diminution of muscle fibers in the cecal wall was found to continue over into the appendix on both medial and lateral walls. Dipping and fusion of the longitudinal muscle fibers into the circular muscle bundles occur frequently and suggested the necessity for making dissections of the disposition of the longitudinal muscle bands of the cecum as they ramify over the appendix.

Dissection of the Taeniae Coli (Longitudinal Muscle Bands) at the Site of Appendicocecal Union.—How the longitudinal muscle bundles of the taenia coli dispersed themselves over the proximal portion of the appendix was studied in 18 cases. The specimens were prepared for dissection by digestion in 0.5 per cent hydrochloric acid solution. Employing a micro-dissector (mag-

* The authors desire to express their appreciation to Drs. E. A. Boyden and E. T. Bell for helpful suggestions and advice in the matter of procedure as well as interpretation. Also to Miss Nancy Harrison, technical assistant in the surgical laboratory, for the studied care with which she executed the difficult and arduous task of cutting thousands of sections.

nification about ten diameters) the serosa was separated readily in most instances from the muscle fibers. The longitudinal muscle bands, when teased apart, appeared to be constituted of three layers, superficial, middle and deep fibers.

The taeniae coli were cut 3 to 4 cm. from the cecal apex and with gentle teasing, the peripheral distribution of the muscle fibers could be readily ascertained. The superficial fibers of the three taenia continued over the appendix as the longitudinal muscle of the appendix. It should be stated here that continuance of the taeniae coli over the length of the appendix as such was not noted in any of the gross specimens available for examination. The deep layer of muscle fibers in the taeniae coli were noted to take various courses about the base of the appendix. In all specimens the deep fibers were found

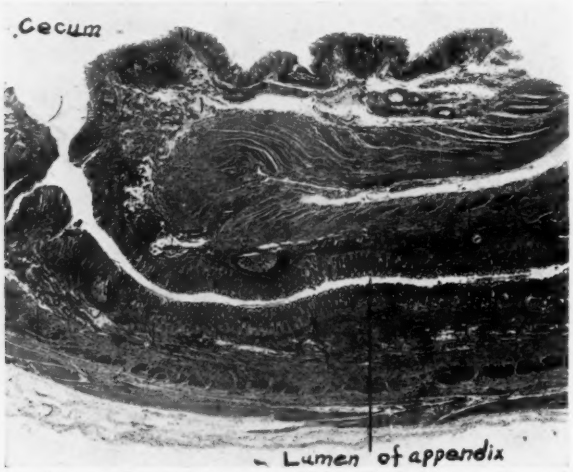

FIG. 4.—On the upper or medial wall of the appendicocecal union, the thickening of the muscle at the apex is apparent—a frequent occurrence.

to be intimately attached to the circular fibers at the cecal apex. In ten instances, all the taeniae sent muscle fibers to encircle the base of the appendix in an iris diaphragm-like manner. In six instances this decussation of the fibers of the taeniae about the appendix was missing. In two instances the anterior taenia divided into a Y-like arrangement sending middle fibers to both lateral and posterior taeniae. The anterior taenia sends the strongest band to the posterior taenia.

II. Resistance to Luminal Outflow from the Vermiform Appendix.—It was the observation of resistance to luminal perfusion of the intact appendix (previously briefly described) which suggested the necessity for an investigation of the anatomic features of the vermiform appendix related above. At the time of appendicectomy, in suitable cases, a No. 19 gauge needle was inserted into the tip of the intact appendix. When the appendix could not be readily delivered, it was found necessary to divide its mesentery first. The needle in the lumen of the appendix was attached to a water manometer in the manner indicated in Fig. 5. The pressure in the system was increased every two minutes by increments of 5 cm. of water, beginning initially with

atmospheric pressure until the resistance to luminal perfusion was overcome and water ran freely into the cecum as indicated by a sudden drop in the column of water in the manometer. Later it was found that the resistance to outflow from the lumen could be determined more quickly by the following means, the results checking closely with the method just described: Fluid was added to the manometer-appendix system by means of an intravenous flask and Murphy drip bulb, the pressure being raised to 80 or 100 cm. of water at the start, forcing fluid on into the cecum, thus washing any possible fecal or foreign matter out of the lumen. Thereafter the flow through the Murphy drip was stopped, and the level to which the meniscus settled above the appendix was termed the absolute resistance to outflow. In the majority of instances the determination was repeated, raising the level very slowly and very close checks were the rule. In some instances, the degree of resistance was determined before cutting the mesentery as well as after, and finally, also immediately after removal of the appendix. In the main, fairly constant levels of pressure were observed in each specimen under these varying conditions. The measurements noted are indicated in Table VI. In the most severe types of acute appendicitis, no determinations of resistance to intraluminal pressure were undertaken until the appendix had been removed.

TABLE VI

RESISTANCE TO INTRALUMINAL PERFUSION *

	No. of Cases	Centimeters of Water Pressure Sustained			
		Average	Median	Maximum	Minimum
1. Normal	11	38.0	28	110	16
2. Interval	45	54.4	45	130	16
3. Acute	27	73.0	68	120	12 †
4. Normal from cadavers	13	2.9	3	7	0

* This table also contains pressure determinations made upon the excised appendix directly after removal.

† This appendix was infested with pinworms; the next lowest readings in this group were four cases with readings of 30 cm.

III. Appendicostomy Studies.—An appendicostomy with delayed opening of the appendiceal lumen was established in fifteen patients with cancer of the bowel.* In another, with ulcerative colitis, a double barreled terminal ileostomy was performed and, simultaneously, appendicostomy. In each instance the appendix was brought out through a stab wound, large enough to obviate compression of the appendix and mesentery. As much as possible of the appendix was exteriorized and fastened to the skin to prevent retraction. During convalescence from the initial operation, the projecting tip of the appendix was amputated, and a No. 8 French soft, urethral catheter (with its end cut squarely off) was inserted into the appendiceal lumen. A tie was placed about catheter and distal appendiceal wall sufficiently tight to preclude discharge around the catheter. As a preliminary measure, to insure the presence of a lumen free from fecal material, 20 cc. of saline solution were washed

* No patient has come to harm through the performance of these appendicostomies.

through the appendiceal lumen into the cecum. In a number of instances, the catheter tied into the lumen of the appendix was pushed into the cecum, to be certain that no strictures were present. In the main, it was found easier to push a catheter into the cecum through the appendiceal lumen than a probe, which was very likely to become engaged in the folds of the mucosa.

The resistance to luminal outflow from the appendicostomies was determined in two ways. In the cases done in the early months of 1936, the method described above with reference to the perfusion of the intact appendix at operation was employed (Fig. 5). During the past ten months, the pressure

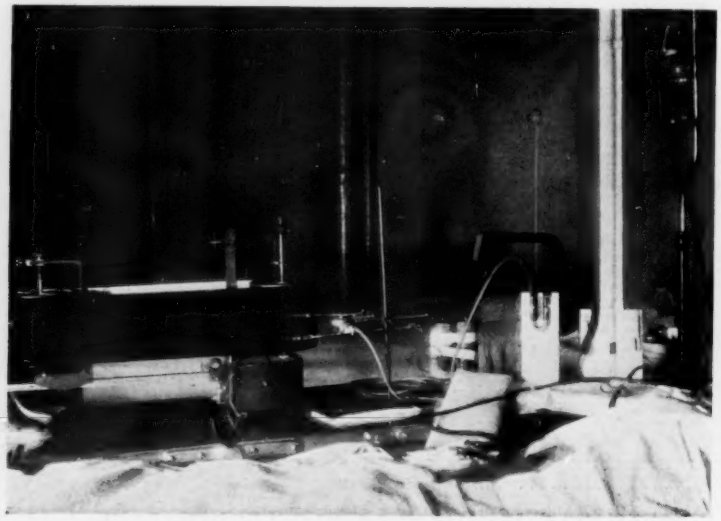

FIG. 5.—The apparatus used in determining the resistance to luminal outflow. In the determinations made in the operating room only the manometer was used. A kymographic record was regularly made in the instance of appendicostomies as shown here.

determinations have been registered directly on very slowly revolving smoked drums, employing a recording float connected directly to the catheter in the appendiceal lumen and a mercury manometer. This apparatus was carefully calibrated and it was observed that the change of volume of the fluid in this closed system, resulting from displacement of mercury and distention of the rubber tubing, necessary to raise the pressure from 0 (zero) to 100 cm. of water pressure was 0.62 cc. The resistance to luminal outflow from these appendicostomies was in general of the same order of magnitude as had been observed in the intact vermiform appendix at operation (Table VII).

TABLE VII

RESISTANCE OF THE APPENDIX IN PATIENTS WITH APPENDICOSTOMY TO INTRALUMINAL PERFUSION

	Centimeters of Water Pressure Sustained			
No. of Cases	Average	Median	Maximum	Minimum
12	47.7	42.0	100.0	8.75

Most of these determinations were made after an interval of five to seven days subsequent to the establishment of the appendicostomy—at which time,

the appendix had become well healed in the wound. To exclude the possibility of pyramiding of the resistance to outflow by the contraction of the healing tissue immediately adjacent to the appendix, an observation was made in one instance two hours following the performance of appendicostomy. An intraluminal pressure of 40 cm. of water was sustained for two hours.

The plan pursued in most instances for the study of the contractile activity of the appendix over a long period of time was as follows: Water was permitted to run into the lumen under the influence of gravity pressure by the drip method at a constant rate, usually 20 drops per minute. The contractile activity of the appendix was recorded quantitatively on the revolving drum. Peaks of activity were observed to come in the fasting patient every seven to 15 minutes, each consisting of one or many momentary rises of

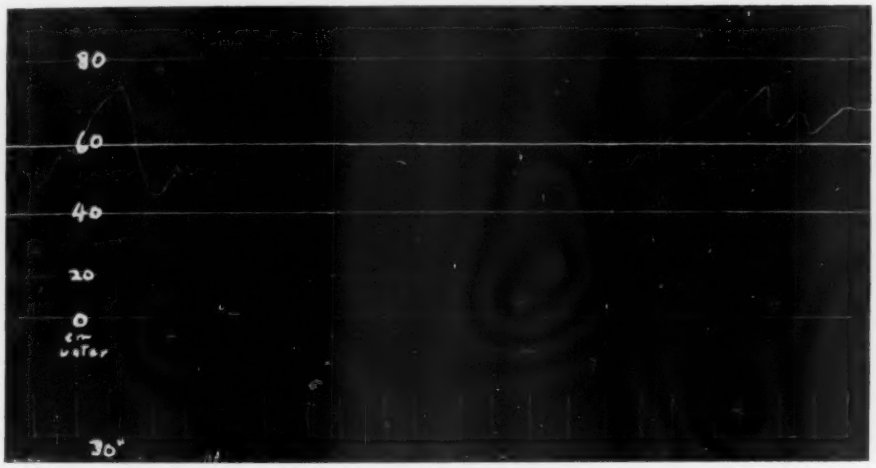

FIG. 6.—On the left margin of this tracing the intraluminal pressure of the vermiform appendix is recorded (appendicostomy); the catheter is then pushed into the cecum with a resultant fall in pressure, which returns again when the catheter is withdrawn once more into the lumen of the appendix, as indicated on the right extremity of the tracing.

pressure to 30 to 50 cm. of water. Between these active periods were intervals when the pressure hovered around 15 to 25 cm. of water pressure. During such intervals, the pressure tracings usually exhibited, every eight to ten seconds, small rises of 2 to 5 cm. increases in pressure.

The patient with ileostomy and appendicostomy afforded an opportunity to record simultaneously cecal and appendiceal pressures, one catheter being in the appendix; the other led into the cecum through the ileum. Whereas the basal pressure in the cecum was 3 to 4 cm. of water, in the appendix it was 15 to 25 cm. In the quiet intervals of the appendix, the cecum was inactive and when the appendix exhibited periods of increased activity, the cecum simultaneously became more active.

In a number of instances, somewhat similar information was obtained by recording the intraluminal pressure of the appendix, then advancing the catheter into the cecum and later withdrawing it again into the lumen of the appendix. The greater contractile activity of the appendix is easily discernible

in Fig. 6. The intraluminal pressure sustained by the ileocecal sphincter, the catheter being tied into the ileum, was found to be 18 to 20 cm. of water.

(2) *Secretion of Fluid by the Appendix.*—The calibrated preparation described above in which entry of 0.62 cc. of fluid into the closed system indicated a pressure rise of 100 cm. of water, supplied a means of investigating fluid secretion by the appendix. The slope of the tracing on the kymographic record indicated the rate of fluid accumulation and from the pressure attained the increases in fluid volume were readily calculated (Fig. 7). In other instances the fluid secreted by the appendix was collected simply by permitting the catheter securely fastened in the appendiceal lumen to drain into a small glass tube properly stoppered and fixed to the dressing.

By both these methods 1 to 2 cc. of a slightly turbid fluid was collected

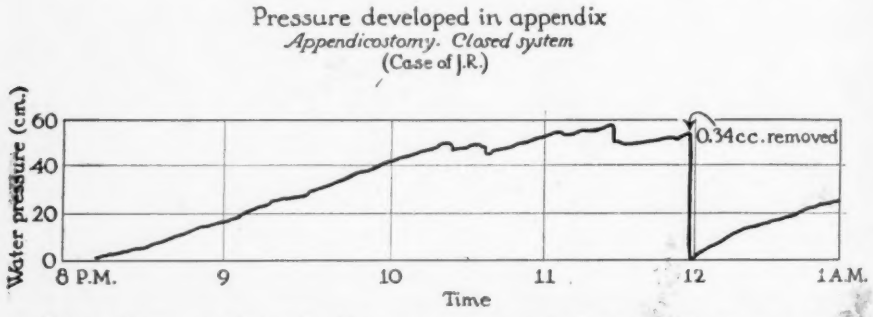

FIG. 7.—Pressure tracing made with a catheter in an appendicostomy. The spontaneous rise of pressure from atmospheric to almost 60 centimeters in four hours is shown. When 0.34 cc. of fluid was aspirated from this closed system, the pressure fell to zero and mounted again. The lumen of the appendix was patent. Secretion of fluid by the appendix only can explain this occurrence. Faradic stimulation will produce temporary elevations which are not sustained. Fluid was also later collected from the appendicostomy in a test tube fastened to the dressing.

every 24 hours. In one instance it was quite clear. It is at once apparent that in either instance, such fluid accumulations do not represent all the fluid secreted, for the opportunity for escape of fluid into the cecum was ever present. Though one cannot wholly exclude the possibility that the fluid came in part from the cecum, it is not believed that such was the case, not alone because of the pressure differences in cecum and appendix, but moreover because of the want of admixtures of cecal content with the fluid collected. The nature of this secreted fluid still remains to be determined.*

(3) *Effect of Drugs upon the Contractile Activity of the Appendix.*—In the main, the effect of drugs was essentially that noted below upon the excised appendix suspended in oxygenated Locke's solution. These findings will be elaborated in a subsequent communication (Dennis). Adrenalin administered subcutaneously or intravenously lowered the base pressure and abolished the contractile waves of activity—spinal anesthesia did essentially the same thing. Amyl nitrite (the fumes of two broken pearls inhaled) was

* Since this paper was written, three cases presented themselves in which a part or all of the appendix could be exteriorized. In these the organ was ligated near the base, following which fluid secretion was evident, pressures being permitted to develop as high as 40 centimeters of water. These experiments definitely exclude the possibility of the fluid having come from the cecum.

without constant effect, as were also benzedrine and atropin. Papaverine was followed by no consistent phenomenon. Morphine sulphate 0.010 Gm. (gr. 1/6) raised the basal pressure and increased the frequency of the smaller waves but decreased their size. Seven cubic centimeters of 3 per cent procaine solution placed in the lumen evoked no effect. Five cubic centimeters of 1 per cent cocaine solution, allowed to drip into the lumen over a five minute interval, caused a smoothing out of the finer waves and raised the height to which the pressure rose at the subsequent peak of activity. Betamethylacetylcholine, 10 mg. given hypodermically, increased the size and frequency of the small waves sufficiently to hold the base line up 10 cm. for several minutes. These observations were made after a period of fasting. The ingestion of food appeared to raise the basal level of pressure and increased the amplitude and frequency of the waves of contraction.

(4) *Placement of Bacteria Obtained from Instances of Acute Suppurative Appendicitis into the Lumina of Appendicostomies.*—Organisms cultured from the appendiceal lumen of two suppurative appendixes were without effect when 2 cc. of such a suspension were slowly injected into the lumina of two patients with appendicostomies. In neither instance was there fever or other reaction attending such injection during the succeeding 48 hours. At the time that the nature of the organism present in the initially inflamed appendixes was determined, *Bacillus coli* in each instance had overgrown the cultures.

(5) *Fate of Birdshot Placed in the Appendicostomy Stoma.*—A No. 9 birdshot (2.79 Mm. in diameter) was placed in the lumen of the appendicostomy in several patients and its position noted roentgenographically. In a few instances, it was extruded on to the dressing. In one instance the shot persisted in the appendix for more than two months. The introduction of bacteria from an instance of acute suppurative appendicitis into the lumen of the appendicostomy with the shot in place was also tolerated without reaction. In one instance the birdshot entered the colon in 24 hours; in another in 36 hours; in yet another in less than two hours. This latter patient suffered cramps as the shot progressed toward the cecum, which ceased after the shot had negotiated this passage.

(6) *Microscopic Study of Segments of Exteriorized Vermiform Appendices Subjected to Increase of Intraluminal Pressure.*—In a number of the patients with a good length of the appendix exteriorized, segments became available for purposes of microscopic study both before cannulation and after long intervals of sustained intraluminal pressure. Because of the serosal reaction attending exposure to the atmosphere, the histologic changes were difficult to evaluate. It was always felt desirable for purposes of safety to allow the exteriorized appendix to become firmly adherent (five to seven days) before prolonged distention was undertaken. This portion of the study will have to await suitable instances in which the whole appendix can be safely exteriorized and subjected early to increases of intraluminal pressure to avoid the complication of serosal irritation.

It may be properly related here, however, that abdominal pain and nausea,

occasionally, and vomiting less commonly, attended long sustained increases of intraluminal pressure. Some of these exhibited slight febrile and leukocytic responses as well.

In this connection, the appendix of one patient is particularly interesting. The exteriorized segment when opened at the tip, five days after the establishment of appendicostomy, appeared unusually distended. Several cubic centimeters of a yellowish-gray pus exuded when its lumen was entered. The mouth temperature was 99.2° F. and the leukocytic count made directly after opening was 13,000. The amputated distal end of the appendix showed evidence of suppuration in the wall. Unfortunately a culture of the extruded pus was not obtained immediately and a culture from the lumen made after a few hours became overgrown with *Bacillus proteus*. The appendicostomy was cannulated and the absolute resistance to outflow determined. At first no fluid could be forced; after eight hours the resistance to outflow was found to be 85 centimeters of water. A catheter was left in the lumen for many days but no evidence of fluid secretion was obtained. Water could be injected into the cecum through the appendiceal lumen with a syringe but a catheter could not be introduced into the cecum. A lipiodol injection revealed two strictures on roentgenologic examination.

IV. Studies upon the Excised Appendix.—(1) *Resistance to Outflow:* It was found necessary to determine the resistance to outflow upon the excised specimen *immediately* after excision, for it was observed when the appendix lay exposed at atmospheric temperature for periods exceeding ten minutes that a gradual decrease in resistance resulted, which became minimal in 30 to 40 minutes. The absence of definite resistance to outflow from the appendix of the cadaver is noted in Table VI, item 4. The determination of the resistance to outflow was therefore made in the operating room directly following appendicectomy. Not uncommonly an increase in resistance over that observed prior to appendicectomy was noted in the excised specimen, due, in some measure probably, to the stimulation of the trauma accompanying excision; for it was noted contraction in length attending excision was not an uncommon circumstance. Control measurements of the length of the appendix before severance of its mesentery and after, as well as following removal, showed that shortening frequently attended these procedures and occasionally by as much as one-third of the total length of the appendix. Great shrinkage in length was accompanied by similar increases in resistance to outflow. In the main, however, these pressures sustained by the excised specimen corresponded fairly well with those observed before removal of the appendix.

It was further noted that when successive segments of 1 cm. in length or less were amputated from the base toward the tip that the resistance to outflow still persisted, and, as a matter of fact, often exhibited increments of gain owing to the greater contraction of the residual portion occasioned by the consecutive cuttings. It was found that this hyperirritability of the excised appendix could be circumvented by placing the specimen in an ice box at a temperature maintained between 2° and 7° C. Then, when the appendix was

suspended in a temperature controlled water bath (37° C.) containing Locke's solution (with glucose eliminated, as suggested by Magnus and Alvarez), kept thoroughly oxygenated, good rhythmic muscular contraction occurred spontaneously. By inserting a cannula into the distal end of the appendix and attaching a thread to the proximal, which in turn ran around a pulley and was fastened to a recording lever, both the changes in length and variations in pressure required to force fluid into the system at a given rate could be graphically recorded. In this fashion it was shown that the rhythmic contractions of the two sheets of muscle are usually synchronous, but that either layer (circular or longitudinal) may contract spontaneously independently of the other. The pressures sustained with such preparations were usually about one-third of those observed just before or immediately after the removal of the appendix.

Appendixes which exhibited evidence of mild inflammation developed strong rhythmic contractions, occasionally greater than those noted in the normal specimens. When the effects of suppuration and damage to the appendiceal wall were plain, however, the contractile activity was feeble; in specimens in which only a portion of its length was involved in the inflammatory process, the healthy part exhibited satisfactory contractile activity, while the former showed no or poor movement. No suggestion of a gradient of activity was observed in these excised appendixes, but this matter will require further study.

A better opportunity, on the whole, was afforded in these preparations for the study of the effect of drugs upon the muscular contractions of the appendix than in the appendicostomies by the simple addition of the chemically pure drug in a certain dilution to the medium of the water bath. This portion of the study will later be reported in detail (Dennis). Briefly it may here be said, the addition of 0.5 cc. of adrenalin hydrochloride (1 : 1000) to the 180 cc. of Locke's fluid in the water bath almost invariably caused a decrease in rhythmic contractions or stopped them entirely, affecting the tone of both muscle layers; the addition of papaverine 0.016 Gm. (gr. ¼) usually, but not always, caused diminution or cessation of movements; benzedrine sulphate in a concentration of 1 : 1000 uniformly increased the tone of both sheets of muscle and tended to accelerate the rhythmic contractions; atropine had a variable effect, in concentrations of 0.013 per cent the tone of the muscle was increased, whereas, in concentrations over 0.025 per cent, paresis occurred. The effect of barium chloride was most marked, a 30 mg. crystal suspended in the bath often provoking rhythmic contractions after futile waiting of two hours or more for them to appear spontaneously. The effect of the application of cocaine hydrochloride (1 per cent) was most interesting when applied to the serosa. All muscular activity stopped immediately; when injected into the lumen, it had a similar but less marked effect, and only after a latent period of about five minutes.

V. Retention of Foreign Material by the Vermiform Appendix.—The retention of birdshot in appendicostomies has already been described. To

investigate the matter further, it was proposed to examine the intraluminal content of the excised vermiform appendix for barium in patients who had previously had a suspension of barium sulphate injected by enema for roentgenographic examination of the colon. At first the flame test was employed to examine for the presence of barium, but it was found to be subject to so many discrepancies that it was abandoned in favor of the spectrophotometric method. With the kind assistance of Dr. Irwin Vigness of the Department of Physiology, the absence or presence of barium in excised appendixes could be readily determined. The entire content of the washed appendix and half of the bisected appendix were ashed over a hot flame in a platinum crucible. The residue was then dissolved in strong acetic acid and the solution was submitted to spectrophotometric examination. The barium lines in the spectrum occur at 45.54 and 23.32 Angström units.

Thirteen appendixes removed from six to 790 days following the administration of barium, in which the appendix was not visualized by roentgenologic examination, failed to show spectrophotometric evidence of barium. In four other instances in which the appendix was visualized by roentgenologic examination and removed after intervals of ten, 13, 93 and 257 days following the barium enema, no spectrographic evidence of barium was found. In six other specimens, however, in which the appendix had been visualized on roentgenologic examination from eight hours to six days prior to appendicectomy, barium was detected by the spectrophotometric method in all. The approximate concentrations of barium in these specimens varied from .05 to 10 per cent. In patients who were known not to have had barium for roentgenologic examination at any time, the removed appendixes and their content showed no trace of barium by this method of examination.

Retention of barium for some time within the appendix has now and then been observed roentgenographically. In the instance of a recent patient with cardiospasm, barium entered the appendix after oral ingestion and when a scout film of the abdomen was made 31 days later, the barium was still present in the appendix. Barium was then again given by mouth without altering the opaque shadow in the appendix. Every ten to 14 days, a film was taken of the cecal region. The barium shadow in the appendix continued to be visualized for 64 days more. If no more barium entered the appendix at the time of the second examination—a plausible inference from the roentgenologic study—barium was retained in the vermiform appendix of this patient for 95 days.

VI. Is Fluid Secreted or Absorbed by the Obstructed Cecal Appendage of Animals?—Many studies have been made on the comparative anatomy of the cecum and its appendage. The studies of Huntington, Kelly and Hurdon and Reider are particularly well known. No study has previously been made with reference to a secretory or absorptive function of this segment of the gut. The evidence related above (Group III, item 2) concerning fluid secretion from the vermiform appendix of man suggested the necessity for making a similar investigation on animals which are readily available. Only the chim-

panzee and the gibbon, according to comparative anatomists, have a true vermiform appendix. Other animals have a cecal appendage which communicates more directly with the cecum. There are, to be certain, many well recognized anatomic variations in form, size and shape of such appendages.

Because of the absorption of water from the intestinal content in the right half of the colon, it might reasonably have been believed that water would be absorbed by an appendage of the cecum. As has been indicated, however, the unobstructed vermiform appendix of man afforded no evidence of water absorption—on the contrary, definite evidence of fluid secretion was obtained. Other animals exhibiting a wide mouthed communication between cecum and its appendage and a larger lumen failed in consequence to exhibit any resistance to outflow from the appendage. In such experiments, therefore, it was necessary to ligate securely the base of the appendage to determine

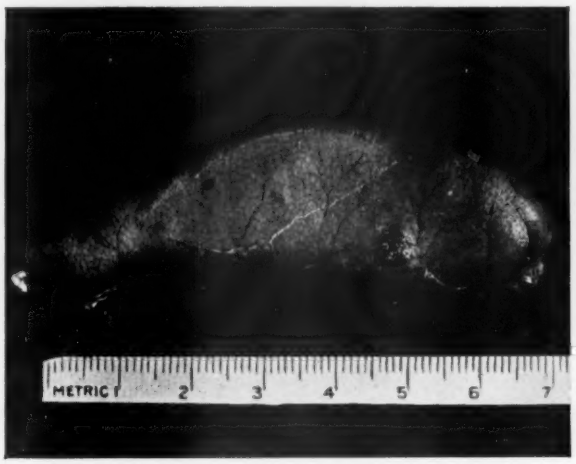

FIG. 8.—Obstructed cecal appendage of rabbit which perforated 5 hours and 18 minutes after the administration of croton oil (Table IX, Rabbit No. 77). The site of perforation near the mesenteric border in the distal third is quite obvious.

whether fluid was absorbed or secreted. The distal tip of the appendage was then cannulated in the same manner that had been employed in the appendicostomies of man. Aseptic technic and intraperitoneal or intravenous pentobarbital sodium anesthesia were employed throughout.

The results of these experiments are extremely interesting and would appear to shed light upon the problem of appendiceal obstruction in man. Only in the cecal appendage of the rabbit was evidence of fluid secretion observed—in all other animals, so far investigated, obstruction of the cecal appendage is not attended by fluid production.

(a) *Obstruction of the Cecal Appendage in the Rabbit.*—Briefly it may be said that almost invariably unmistakable evidence of rapid fluid secretion accompanied obstruction of the cecal appendage. In ten to 14 hours, the intraluminal pressure had increased because of fluid production to the extent that rupture occurred. When croton oil (three minims) was administered

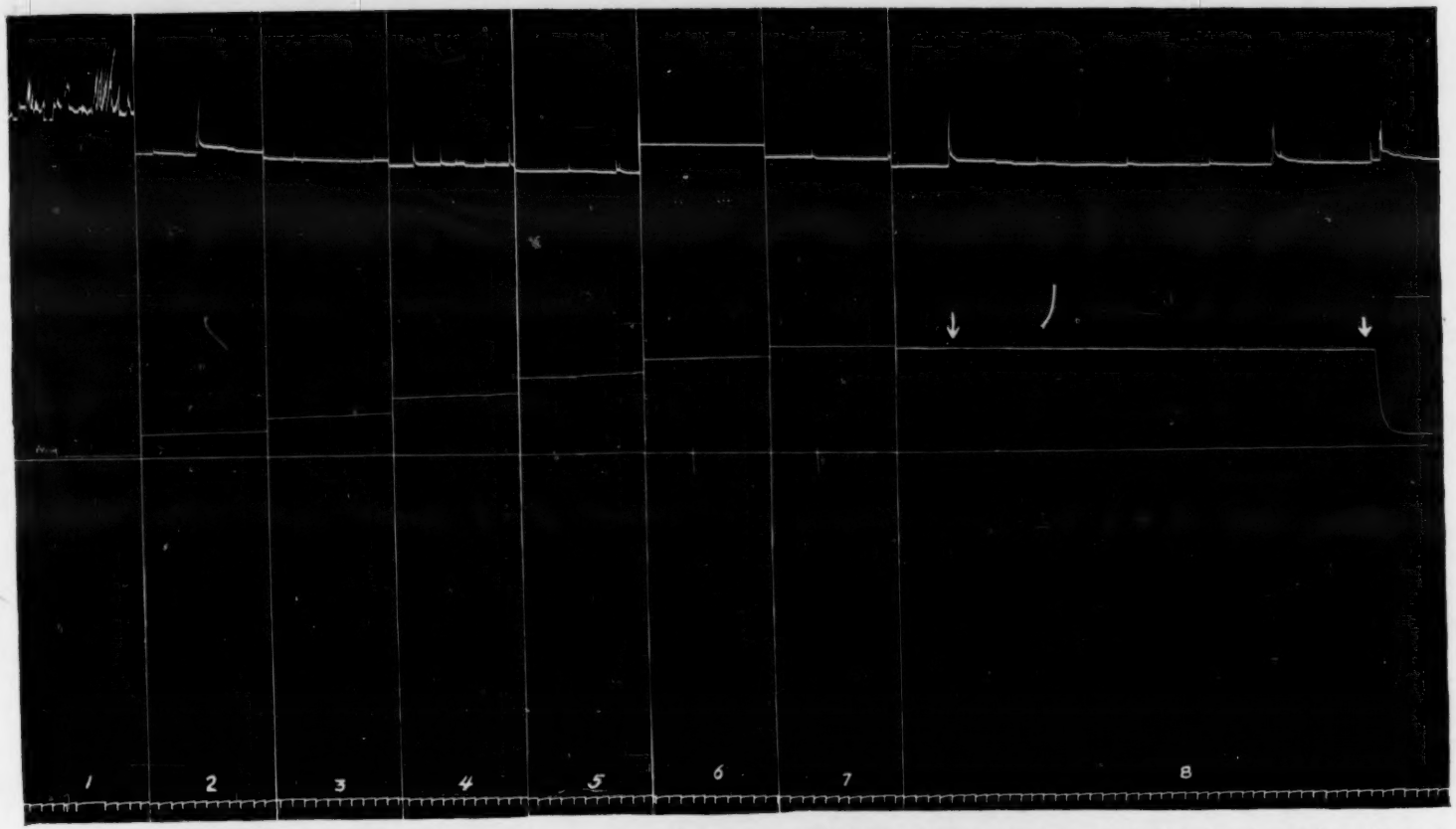

FIG. 9.—Kymographic tracing of hydrostatic changes in obstructed cecal appendage of Rabbit No. 46 (Table VIII). (1) Irrigation of cecal appendage with 25 cc. of Ringer's solution, followed by ligation of the base. (2) Three hours after ligation. Pressure 16.3 centimeters water. (3) Four hours after ligation, hydrostatic pressure 24.4 centimeters of water. (4) Five hours after ligation, pressure 38.0 centimeters of water. (5) Six hours, pressure 50.0 centimeters of water. (6) Seven hours, pressure 59.4 centimeters of water. (7) Eight hours, pressure 68 centimeters of water. (8) Nine hours after ligation, pressure 66.0 centimeters of water. Tear occurred in the serosa as indicated by the arrow. Note the respiratory change at the time of the serosal tear and rupture of the wall. Rupture 9 hours and 35 minutes after ligation. The respirations are indicated above; the arrow at the left indicates the second tear, the one at the right, the fall of the pressure to the base line. The marks of the signal magnet are spaced one minute apart.

by gavage, rupture occurred in considerably shorter time (Fig. 8 and Table IX, Rabbit No. 77); earlier perforation was particularly striking after the injection of hypertonic saline solution intravenously (0.3 Gm. of sodium chloride per kilo—a 15 per cent solution being employed). The effect of other drugs has also been investigated but will not be reported upon here. When the artery to the cecal appendage or the artery and vein were ligated, rupture did not attend simple obstruction of the cecal appendage nor even after croton oil (orally) or hypertonic intravenous saline solution was given. The results of these various procedures are indicated in Tables VIII and XI. The gradual rise of intraluminal pressure attending obstruction and the effect of perforation are illustrated in Figs. 9 and 10A.

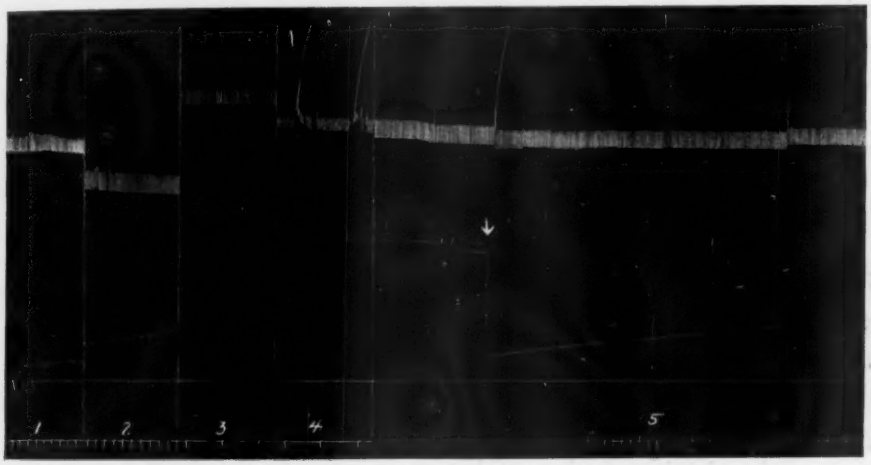

FIG. 10A.—The effect of the intravenous injection of hypertonic saline solution upon the intraluminal pressure of the obstructed cecal appendage of the rabbit (Table X, No. 91). (1) Intravenous injection of 2.2 cc. 15 per cent solution of sodium chloride 20 minutes after ligation; pressure 13.0 centimeters of water. (2) Thirty minutes after hypertonic saline; pressure 34.3 centimeters of water. (3) Pressure 90 centimeters of water one hour after hypertonic saline solution. (4) Two hours after saline solution; pressure 136 centimeters of water. (5) Rupture of the wall of the cecal appendage 3 hours and 30 minutes after obstruction by ligation. Removal of the specimen 2 hours and 30 minutes after rupture.

In a number of other instances the cecal appendage of the rabbit has merely been tied off, and at intervals of from two to 48 hours, the abdomen has been reopened and the appendage has been inspected or excised for purposes of study (Fig. 11). Perforation and sealing off by the adjacent mesentery or mesentery to close the perforation in the wall of the cecal appendage during coils of bowel are common occurrences.* The ineffectual effort of the adjacent mesentery to close the perforation in the wall of the cecal appendage during the course of a pressure experiment is well illustrated in Fig. 10A.

* Since this paper was written, a paper by Mr. A. Q. Wells of St. Bartholomew Hospital in London has appeared in the British Journal of Surgery, April, 1937, in which it is suggested that obstruction of the cecal appendage of the rabbit is without effect—that it is injury to the mucosa that is the important determinant in bringing perforation about. We have as yet not investigated how fluid production is influenced by mucosal injury, but it is difficult to follow Mr. Wells' deductions made from his own experiments in which he relates the appearance of abdominal masses accompanying obstruction of the cecal appendage of the rabbit.

TABLE VIII

INTRALUMINAL PRESSURE RISES AND EFFECTS ATTENDING OBSTRUCTION OF CECAL APPENDAGE OF THE RABBIT

No. of Rabbit	Procedure	Variation	Duration in Hours	Pressure in Cm.	Volume in Cc.	Cc. Output* per Minute	Rupture	Microscopic Study
R-48	Washed. Incannulated. Obstructed		8.17	71.9	14.64	.0298	Yes	Acute
R-39	Washed. Incannulated. Obstructed	Ileal vein injured	10.00	68.0	13.6	.0226	Yes	Gangrenous
R-46	Washed. Incannulated. Obstructed		10.00	60.4	12.08	.0201	Yes	Acute
R-49	Washed. Incannulated. Obstructed		11.00	55.7	11.44	.0188	Yes†	Gangrenous
R-43	Washed. Incannulated. Obstructed		17.17	42.7	8.54	.0082	Yes	Acute
R-50	Washed. Incannulated. Obstructed	Spontaneous production of fluid	2.25	20.0	4.0	.0296	No	Reactive appendix. Serositis
R-42	Washed. Incannulated. Obstructed	Spontaneous production of fluid	3.16	18.5	3.7	.0194	No	Reactive appendix. Serositis
R-40	Washed. Incannulated. Obstructed	Fluid removed at 23 cm.	7.3	22.8	9.76	.0208	No	Serositis
R-35	Washed. Incannulated. Obstructed	Spontaneous production of fluid (fluid twice removed)	10.0	39.0	12.62	.0191	No	Acute
Average of ruptured cases.....			13.26	60.0	12.06	.0195		
R-63	Washed. Incannulated. Not obstructed	Control experiment	10.0	0	0	0	No	Normal appendix. Serositis

* Rate of fluid production is prorated over the entire time period, even though the rate of rises in pressure varied somewhat.

† Microscopic rupture.

The histologic reaction in the cecal appendage of the rabbit attending spontaneous perforation in consequence of obstruction of the cecal appendage is not very much different from that observed in the spontaneous occurrence of suppurative appendicitis in man. A microscopic section near the site of

perforation in rabbit No. 91 (Table X) is shown in Fig. 10C. A drawing of the same specimen is illustrated in Fig. 10B. This interesting portion of the study will be elaborated upon later.

TABLE IX

OBSTRUCTION OF CECAL APPENDAGE OF RABBIT AND ORAL ADMINISTRATION OF CROTON OIL (THREE MINIMS)

No. of Rabbit	Procedure	Variation	Duration in Hours	Pressure in Cm.	Volume in Cc.	Cc. Output per Minute	Rupture	Microscopic Study
R-77	Washed. Incannulated. Obstructed	Croton oil, 3 minims, orally	5.3	69.3	13.86	.0446	Yes	Acute
R-76	Washed. Incannulated. Obstructed	Croton oil, 3 minims, orally	6.0	54.4	10.9	.0363	Yes*	Acute

* Microscopic rupture.

TABLE X

OBSTRUCTION OF CECAL APPENDAGE OF RABBIT ACCOMPANIED BY INTRAVENOUS INJECTION OF HYPERTONIC SALINE SOLUTION

No. of Rabbit	Procedure	Variation	Duration in Hours	Pressure in Cm.	Volume in Cc.	Cc. Output per Minute	Rupture	Microscopic Study
R-91	Washed. Incannulated. Obstructed	⅓ Gm. NaCl per kilo in 15% solution injected intravenously	3.0	136.0	27.2	.1510	Yes	Acute, gangrenous (See Fig. 10A)
R-83	Washed. Incannulated. Obstructed	The same as above	6.0	40.8	8.16	.0340	Yes*	Acute
R-89	Washed. Incannulated. Obstructed	The same as above	7.2	30.0	6.0	.0139	No	Acute (anesthetic death)

* Microscopic rupture.

(b) *Obstruction of the Cecal Appendage in the Dog.*—That obstruction of the washed cecal appendage of the dog is well tolerated has previously been noted (Wangensteen and Bowers). It was proposed to determine here

TABLE XI

OBSTRUCTION OF CECAL APPENDAGE OF RABBIT AND LIGATURE OF ARTERY AND VEIN OF APPENDAGE

No. of Rabbit	Procedure	Variation	Duration in Hours	Pressure in Cm.	Volume in Cc.	Cc. Output per Minute	Rupture	Microscopic Study
R-78	Washed. Incannulated. Obstructed	Croton oil orally. Ligation of artery and vein	5.5	0	0	0	No	Normal appendix
R-79	Washed. Incannulated. Obstructed	Castor oil orally. Ligation artery and vein	18.5	0 (Pressure maintained 9 to 12 cm.)	0	0	No	Acute appendix
R-36	Washed. Incannulated. Obstructed	Ligation appendiceal artery and vein	21.0	0 (Pressure raised to 16.0 cm. when no fluid was produced)	0	0	No	Acute appendix
R-75	Not washed. Obstructed. Not incannulated	Ligation vein and artery and ⅓ of mesentery	Expired 24 hrs.	0	0	0	No	Normal appendix. Traumatic serositis

whether fluid production accompanied this procedure in the dog. As will be observed in Table XII, neither perforation nor evidence of fluid production attended obstruction of the cecal appendage of the dog.

TABLE XII

OBSTRUCTION OF CECAL APPENDAGE OF THE DOG

No. of Dog	Procedure	Variation	Duration in Hours	Pressure in Cm.	Volume in Cc.	Cc. Output per Minute	Rupture	Microscopic Study
D-51	Washed. Incannulated. Obstructed		16.0	8 to 24	0	0	No	Acute
D-54	Washed. Incannulated. Obstructed		50.0	16 to 24	0	0	No	Acute

(c) *Obstruction of the Cecal Appendage and Determination of Secretory Pressure in Other Animals.*—The cecal appendage has been obstructed in three monkeys and the cecal pouch in three pigs and the occlusion was tolerated without perforation or evidence of fluid secretion. In two of the monkeys and two of the pigs, secretory pressures were determined over quite long intervals.

In one monkey an intraluminal pressure of 12 cm. of water developed. In the pigs, water appeared to have been absorbed. The cecal appendage was obstructed in two rats, one cat, and two guinea-pigs—all of which tolerated the procedure well. The cecal pouches of three chickens and two pigeons were obstructed. There was no evidence of inflammation and the procedure was well tolerated.*

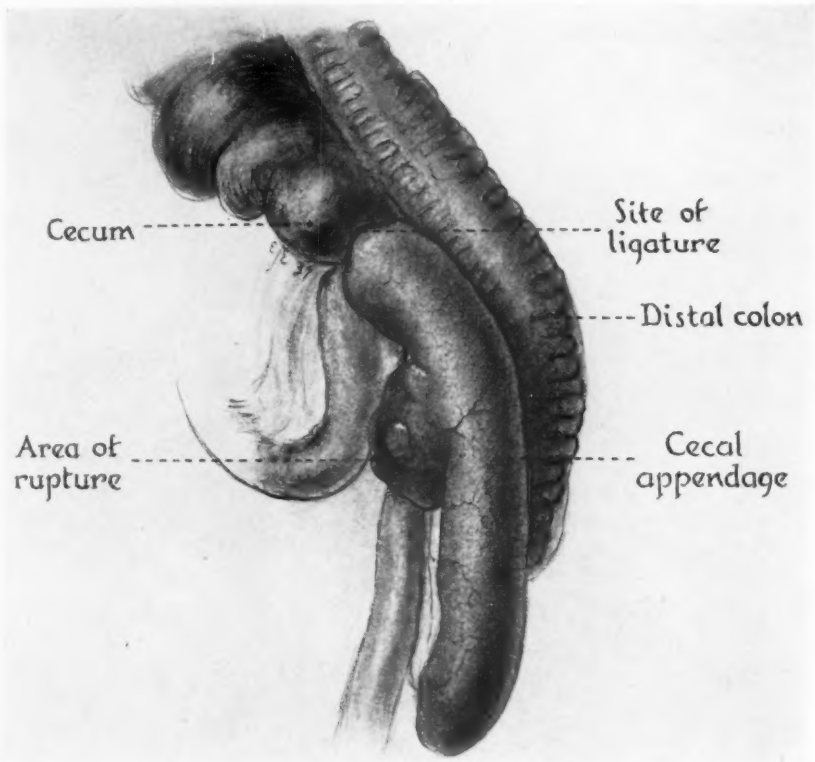

FIG. 10B.—The sealing over the site of rupture temporarily stems the fall in pressure as indicated in 10A, but that the walling-off is ineffectual is also apparent in the fall in pressure at the extreme right of the tracing (10A).

VII.—The Luminal Volume of the Appendix.—Whereas the length and thickness of the appendix have been determined in scores of studies, no observations on the volumetric capacity of the vermiform appendix have come to our attention. When the secretory behavior of the appendix is appreciated, it is immediately apparent that the capacity of the appendix in the presence of obstruction becomes a matter of great importance.

The volume of the cylindrical vermiform appendix has been determined in three ways:

(1) In three freshly excised appendixes, two per cent liquefied gelatin

* Recently we have found that the appendage of the calf, the duck, the striped gopher, the goose, the porcupine, the sheep, and the grey squirrel absorb Ringer's solution, while the appendage of the rat secretes at pressures below seven centimeters of water. In the red fox neither secretion nor absorption could be demonstrated.

(specific gravity 1.028) was gently injected from beneath into the suspended viscus through a needle inserted through the tip. When gelatin came out through the proximal end, the entire specimen was chilled in the refrigerator, the point of needle puncture being sealed by freezing with ethyl chloride. Later, the wall of the appendix was slit open and the appendix itself was dissected free from the gelatin, which weight was then carefully determined. The weight of the gelatin divided by its specific gravity determined the volume. The values determined for the volume of the cylinder in these instances were 0.357, 0.226, and 1.020 cc. respectively.

(2) In ten other formalin-fixed specimens, obtained at necropsy from patients varying in age from six months to 71 years, the volume was deter-

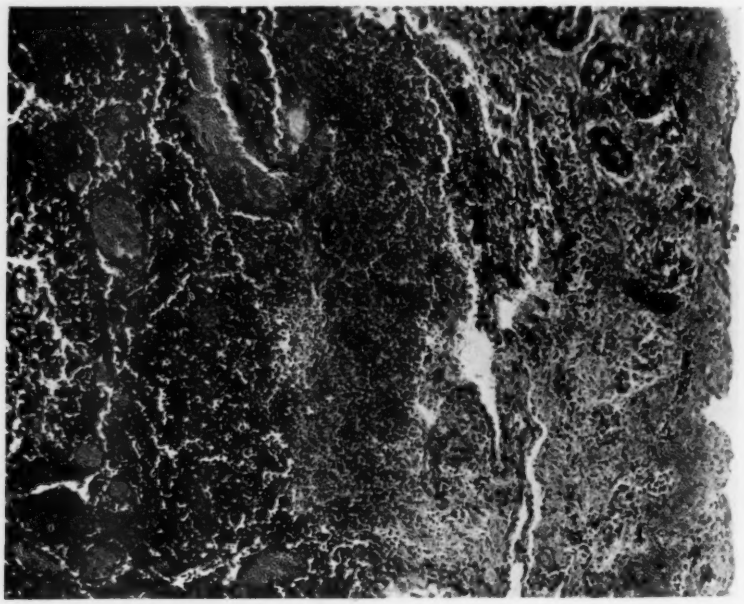

FIG. 10C.—The histologic reaction attending spontaneous rupture which occurred 3 hours and 30 minutes after obstruction of the cecal appendage. The specimen was removed and fixed for microscopic study six hours after the establishment of obstruction. The cytologic response is largely polymorphonuclear and extends through all the walls. A good portion of the mucosa is lost through ulceration. The section is taken in juxtaposition to the site of rupture.

mined in the following manner: The appendix was dried by rolling it in gauze and then milking it out gently. The appendix was then suspended in the manner of the group just described above and water was injected slowly through the tip with a No. 20 gauge needle and a tuberculin syringe. The volume of the appendix was indicated by the fluid injected when water appeared at the top. The average value for the volume of the vermiform appendix in this group was 0.10 cc.; the maximum was 0.24 cc., and the lowest reading, 0.00 (zero). The median value was 0.08 cc. The pressures employed were not measured.

In a group of eight vermiform appendixes obtained at autopsy and then placed in saline solution in an electric refrigerator for a few hours, an at-

tempt was made to rupture the appendix and determine the volume at the time of rupture. The proximal end of the appendix was closed with a hemostat and water was injected through a No. 20 gauge needle in the tip by means of a 20 cc. Luer syringe. In one instance the appendix could not be ruptured by this means; in two others, the serosa tore and fluid oozed through. The average volume at rupture was 5.87 cc.; the median volume was 5.50 cc.; the maximum at rupture was 9.50 cc., and the minimum was 3.0 cc. The pressures employed were not measured, but were, of course, enormous.*

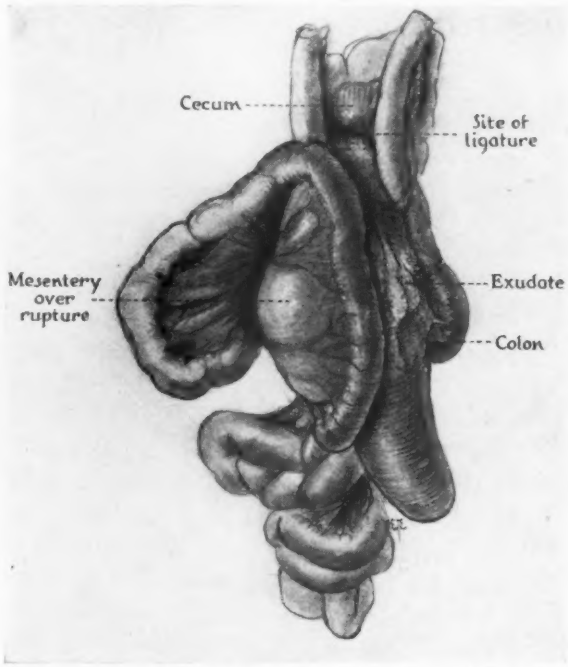

FIG. 11.—Perforation of obstructed cecal appendage of the rabbit. The site of rupture had become sealed over by the mesentery of the ileum. There is exudate on the free serosal surface of the appendage. Finding at reoperation 48 hours after the establishment of obstruction.

(3) The methods described above took no note of the pressure employed at the time of filling of the appendix, so its volume was determined, in eight appendixes (either at operation or immediately after excision, and in one postmortem specimen), in the following manner: The resistance to luminal outflow from the appendix was first determined and the lumen was then irrigated until the fluid returned fairly clear. Any residual content was then gently milked out. A hemostat was applied across the proximal end at the site of amputation and the needle in the distal tip was connected by means of a Y tube to both a water manometer and a syringe (Luer). The volume change in the entire system with changes in pressure could then be readily observed (Table XIII).

* The authors wish to acknowledge the helpful assistance of Mr. P. Beckjord and Mr. H. Svien, both senior medical students, in this and other phases of the work.

TABLE XIII

LUMINAL VOLUME OF THE APPENDIX AS RELATED TO PRESSURE*

Volume at Varying Degrees of Water Pressure.

	Atmospheric (zero)	20 cm.	60 cm.	100 cm.
Normal (four):				
Average	0	0.07 cc.	0.52 cc.	1.4 cc.
Maximum	0	0.18	0.7	2.0
Minimum	0	0	0.35	0.9
Acute, mild (three):				
Average	0	0.07 cc.	0.2 cc.	0.6 cc.
Maximum	0	0.23	0.6	0.9
Minimum	0	0	0	0
Interval (one)	0	0.05 cc.	0.05 cc.	0.3 cc.
Postmortem (one)	0	0.55 cc.	1.15 cc.	1.7 cc.

* From these readings it is apparent that no fluid can be forced into the appendix until the resistance to luminal outflow has been overcome. At atmospheric pressure therefore, the luminal capacity of the appendix is zero.

The findings by these three methods are essentially in agreement. It is evident that the volume of the appendix at physiologic pressures (60 cm. of water or below) did not exceed 0.7 cc. and at 20 cm. pressure the luminal capacity did not exceed 0.23 cc. in the intact appendix.

It has been indicated in Tables VIII and XI that the obstructed cecal appendage of the rabbit may burst at relatively low pressures (40 to 70 cm. of water). The normal cecal appendage of the rabbit (not subjected to spontaneous rises of intraluminal pressure attending obstruction) will burst at pressures from 120 to 150 cm. of water. The increases in intraluminal capacity attending the slow process of spontaneous distention varies under the influence of obstruction.

It has been observed that the excised, unruptured, gangrenous vermiform appendix of man may also rupture at relatively low pressures—in one instance at 20 cm. of water and in another at 70 cm. The excised normal appendix of man, however, when subjected to sudden increases of intraluminal pressure could not in a single instance be ruptured by pressures as high as 2400 cm. of water (approximately 2.3 atmospheres). In this process, a stretch to a luminal capacity of about 5 cc. occurs.

The implications in part are plain, *viz.*, that the luminal capacity of the vermiform appendix of man is much smaller than that of the cecal appendage of the rabbit, and that the bursting strength of the latter is considerably less than that of the appendix of man. It would appear therefore that interference with blood flow which results from maintained intraluminal pressure exceeding the capillary pressure brings about necrosis of the wall, which in turn accounts for perforation or gangrene of the obstructed vermiform appendix of man.

In 13 rabbits the thickness of the musculature was determined, also the thickness of the entire wall as well as the diameter of the lumen and the

diameter of the cecal appendage, from formalin-fixed sections cut at the points of juncture of middle and distal thirds (Table XIV).

TABLE XIV

MEASUREMENTS OF THE NORMAL CECAL APPENDAGE OF THE RABBIT, IN MILLIMETERS

	Thickness of Musculature	Thickness of Wall	Diameter of Lumen	Diameter of Appendage
Average of 13 specimens....	0.0213 Mm.	1.53 Mm.	4.86 Mm.	8.15 Mm.

In a group of cases from the postmortem series, similar measurements were made upon the vermiform appendix of man (Table XV).

TABLE XV

THE MEASUREMENTS OF THE VERMIFORM APPENDIX OF MAN IN MILLIMETERS (KELLY AND HURDON)

Thickness of musculature.....	0.4 to 0.8 Mm.
Thickness of wall.....	1.0 to 2.5 Mm.
Diameter of lumen.....	1.0 to 3.0 Mm.

Kelly and Hurdon quote the diameter of the vermiform appendix as determined by seven other authors. Among these measurements there is a variation in diameter from 3 to 8 Mm. The average is 5.2 Mm. and the median value is 6 Mm. It is readily apparent, therefore, that the wall of the rabbit's cecal appendage is thinner than that of man, whereas the total diameter is greater—accounted for largely by the presence of the greater lumen.

SUMMARY

The nature of the appendicocecal union has been described (Table I). In about 80 per cent of instances a mucosal cecal fold (Gerlach's) overlies the superior aspect of the appendiceal orifice. Only rarely does this fold contain muscle fibers. None were observed in adult specimens and in 63 fetal and infant specimens studied, this occurrence was noted three times. The appendiceal orifice varies considerably in size and persists after appendicectomy, as do also the cecal folds. At the apex of the union between cecum and appendix there is a thickening of the muscle on the medial aspect of the superoir wall (Fig. 4). No true evidence of a distinct circular sphincter muscle has been found. It is to be stated, however, that the circular fibers, considering the size of the appendiceal lumen, constitute a generous sheet of muscle whose action is sphincter like.

The vermiform appendix exhibits a definite resistance to luminal outflow —the extent of which is apparently a resolution of the amount of circular muscle in its wall and the diameter of the lumen. It is by no means a property confined to the appendix but is also possessed by the ureter, vas deferens and other viscera with a small lumen and muscular walls. This resistance to luminal outflow, as studies continued over a long period of time in appendicostomies have shown, varies from hour to hour and in turn can be modified by the employment of drugs. In freshly excised appendixes it was shown that the application of a dilute solution of cocaine to the exterior largely abolishes this resistance. Application of cocaine to the interior is less effective. This

observation would suggest that the circular muscle and Auerbach's plexus are largely accountable for this property. Meissner's submucous nerve plexus apparently has less to do with it and there is no suggestion that the argentaffine cells in the crypts of Lieberkühn play any rôle in this behavior of the appendix. The extent to which the appendix may retain foreign bodies has been briefly reviewed.

Evidence of fluid secretion by the vermiform appendix was also obtained. The nature of this secretion still remains obscure. Its amount in the unobstructed appendix would appear to be from 1 to 2 cc. a day. Of a large number of animals, the function of whose cecal appendages were investigated, only in the rabbit has evidence been found of marked fluid secretion. It has been pointed out that rupture of the rabbit's appendage when obstructed will occur in ten to 14 hours and that this occurrence can be hurried considerably by the intravenous infusion of hypertonic saline solution or by the oral administration of croton oil. It is believed that this result is largely an effect of fluid secretion—muscle contraction is less responsible than the dilating force of secreted fluid. The luminal capacity of the vermiform appendix was found to be astonishingly small and relates itself intimately to the problem of fluid secretion under conditions of luminal obstruction.

Discussion.—In the light of the knowledge that the vermiform appendix of man secrets fluid, its behavior under conditions of obstruction becomes understandable. Whereas, it may have been more readily believed that this segment of the intestinal canal, so intimately related to the colon, should be identified with absorption,* the demonstration of its secretory function, even though it be slight, lends trustworthy credibility to an obstructive origin of appendicitis. It is not without interest that only the vermiform appendix of man and the obstructed cecal appendage of the rabbit of species thus far investigated exhibit this property. Both possess a generous deposit of lymphoid tissue in the mucous and submucous coats of the bowel.

That the vermiform appendix of man may become easily obstructed is obvious. How this obstruction may come about is not so readily discernible. That appendicoliths (whose exact origin yet remains to be explained) and foreign bodies may obstruct the lumen of the appendix is a matter of common experience. How the appendix may become totally obstructed in other manners still demands explanation. That swelling of the mucous and submucous lymphoid tissue may bring about obstruction of the lumen appears reasonable; that augmentation of the normal physiologic obstruction to emptying by reflex nervous causes may initiate circulatory damage to the appendiceal mucosa and set in motion the effects of continued luminal obstruction would seem to be not unlikely.

Why the lumen of the vermiform appendix of the older child, adolescent, or adult becomes more easily obstructed than that of the newborn or child

* It is likely that at every level of the intestinal canal, fluid is secreted and absorbed. Secretion is preponderately the function of the upper intestinal segments—absorption of the lower. In the appendix, this balance is in favor of secretion in that viscus.

under one year of age is understandable after considering the findings in Table I, in which the larger communication between appendix and cecum is indicated. Nagoya observed, with advance in years, a decline not only of the mucous and submucous lymphoid tissue of the appendix, but also a decrease in number of the intestinal glands—findings which would suggest that the mechanism for production of fluid by the appendix became less efficient with increase in age, when appendicitis is also less commonly observed.

A closed loop in which secretion occurs would appear to be particularly hazardous when the luminal capacity is small, as it is in the vermiform appendix. Burget and Dragstedt and their associates have indicated how temporary aspiration of a closed loop, or preliminary washing of it, may permit of its being tolerated with the avoidance of rupture. Undoubtedly the same holds true of the vermiform appendix. With gradual development of obstruction or obliteration, undoubtedly complete luminal obstruction may be withstood without rupture. The alteration of the normal secretory function of the vermiform appendix which comes about through such circumstances accounts for this paradox—an occurrence well known to all who have experimented with closed intestinal loops.

CONCLUSIONS

The vermiform appendix of man serves no known useful function. It apparently does have a function, however, *viz.*, the secretion of fluid. In this function lies the explanation of why the appendix is a treacherous organ when obstructed. What the nature of the fluid secreted by the appendix is, has, as yet, not been determined. How the lumen of the appendix may become obstructed in the absence of an evident cause yet remains to be demonstrated.

The minute anatomy of the vermiform appendix as it bears on the problem of acute appendicitis has been broadly studied. The resistance to luminal outflow which the appendix exhibits is in all likelihood a resolution of its small luminal capacity and strong sphincter-like circular muscle. No evidence of a true cecoappendiceal sphincter has been found.

The effects of obstruction of the cecal appendage have been studied in many animals; only that of the rabbit has so far been found to possess a secretory function similar to that evidenced in the vermiform appendix of man.

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DISCUSSION.—DR. HUBERT A. ROYSTER (Raleigh, N. C.): In my opinion, this is a very important paper. These studies are leading to what has been long admitted to be certainly a predisposing, if not a determining, cause of

most cases of appendicitis, that is, obstruction. We cannot get anywhere in bringing about a reduction of a supposed high mortality in acute appendicitis unless we go behind the returns. For many years I have been interested in the anatomy, physiology and pathology of appendicitis, rather than in the study of technic, which should never get to the point of having a "brilliant surgeon" save somebody's life.

Anatomy, of course, goes back to embryology for its foundation. Doctor Wangensteen's studies, it would seem to me, upon the anatomic basis, are very sound. Embryologic study of the appendix causes us to admit one fact, that it is a so called vestigial organ. As far back as we can ascertain, the appendix was as large as, if not larger than, the cecum, and when the intestinal canal elsewhere underwent highly specialized growth to take care of what was probably the function of the appendix itself, nature began to lop it off, as in all rudimentary and retrogressive organs.

I still believe that the appendix has a function. The first research, undertaken many years ago, was to prove, I think, what Doctor Wangensteen has demonstrated so satisfactorily, that it has a secretory function. Some felt there was a secretion poured into the cecum for the purpose of helping the admixture of feces; others, that probably a fluid was abstracted from the cecum. It remained for Adami and McCrae, in 1914, to show that the appendix is the hydrostatic agent which initiates peristalsis in the colon. This explains constipation in the bedridden; it explains a desire for normal evacuation upon arising, or after taking the first meal; it explains constipation following some interval removals of the appendix; and it also explains some cures of constipation after the removal of a pathologic appendix.

The interesting thing to me about this, and Doctor Wangensteen stressed it, is the secretion of fluid by the appendix. I am absolutely convinced myself that whatever distends the appendix, either from the inside or the outside, is frequently the actual cause of appendiceal attacks.

It was shown by previous investigators, in 1921, in experiments on rabbits, that a fixed or abnormal position of the appendix with adhesions was a factor. A disturbed blood supply, to which Doctor Wangensteen referred, with kinking and obstruction of the vessels, is sometimes necessary to produce a gangrenous appendix. Even with all the obstruction that you might get, you would probably not get gangrene unless the artery of the appendix was occluded by thrombosis, and we have actually demonstrated in many cases the appearance of a thrombus in the meso-appendix, with gangrene below the point of obstruction throughout its whole extent.

It is quite often noted in perforated appendices that we will find fecal concretions either in or outside the appendix, which may go to prove the obstructive theory. The question of fecal concretions as an exciting cause of obstruction or distention is very interesting. It seems to me that upon this question hinges the whole pathology of appendicitis. We cannot understand any disease without a knowledge of its pathology. Upon pathology depends physiology, and behind both is anatomy.

This makes me feel sure that this study is very important; because it compels us to recognize that appendicitis is a going concern, a continuing process, and that all of these factors which Doctor Wangensteen has demonstrated are forerunners of what you and I call the acute attack. I maintain that the acute attack is *not* the disease, only a knock at the door saying, "Let me out," and that in every case that comes to operation, the disease has existed a matter of two or three years, with clinical signs which might be obscure or certain.

I further believe that once appendicitis, always appendicitis, until the

little assassin is executed. I believe also that the study of these factors is going to do more to reduce our death rate, because it will prove absolutely that the conditions that we see at the operating table in the acute attack mean that the disease has existed previous to what we call the fulminating attack; otherwise, we know that certain things couldn't have happened. An appendix which is perforated early, following the first pain, in many cases is called the "first" attack, but in most cases it is the "worst" attack.

Dr. Owen H. Wangensteen (Minneapolis) closing: I believe it can truthfully be said that the appendix has a function; it does not, however, appear to be a useful one. This humble but treacherous occupant of the peritoneal cavity, to employ a characterization of Charles Dickens, may well be called the "Uriah Heep of the Abdomen." The suggestion of Doctor Royster that the vermiform appendix *must* have been previously diseased to give rise to acute suppurative appendicitis does not agree with my conception of the origin of the disease. As a matter of fact, one would anticipate more devastating effects of luminal obstruction upon the normal than upon a previously diseased appendix. Knowledge of the behavior of closed intestinal loops will serve to clarify this point. Several members of this organization, particularly Doctors Dragstedt and Morton, have worked with such loops and have been able to show that the physiology of a loop at certain levels may be modified by aspiration, lavage, and previous drainage of the loop. Every section of the gut probably *absorbs* and *secretes* fluid. In the duodenum, the function is preponderantly secretory. In the vermiform appendix it is more evenly balanced, but yet secretion would appear to be the predominant characteristic. That obstruction of the vermiform appendix may exist without giving rise to acute suppurative appendicitis is readily understandable in the light of how the function of a closed loop may be modified by various factors. Obstruction of the lumen in a previously healthy appendix, however, is undoubtedly always serious.

There is an experimental study of appendicitis by Mr. A. Q. Wells, reported in the April, 1937, issue of the British Journal of Surgery. Many of you will see this article. Our conclusions appear to be in direct conflict with those of Mr. Wells, who concludes that luminal obstruction of the cecal appendage of the rabbit is without significance—that it is the injury to the mucosa which is the important and determining factor. I would conclude from his own experiments, however, that luminal obstruction to the cecal appendage of the rabbit is hazardous. It would appear likely that when Mr. Wells perforated the cecal appendage of the rabbit beyond the ligature with a needle and scratched the mucosal interior that as fluid accumulated in the appendage incident to obstruction, escape occurred along the needle track before the adjacent tissues had an opportunity to wall off the site of leakage, as they can do quite effectively in the perforation attending ligature of the base of the cecal appendage. Whether mucosal injury slows or hastens the secretion of fluid within the obstructed lumen must, of course, be determined by actual experiment.

We have not had an opportunity to determine whether the function of the vermiform appendix in the higher apes such as the chimpanzee or the gibbon, like that of man, and the cecal appendage of the rabbit is more secretory than absorptive. I am inclined to believe that a study of the comparative physiology of this segment of gut in many animals may throw considerable light on the origins of appendicitis in man.

THE REPAIR OF PERIPHERAL NERVE INJURIES

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REPAIR of extensive destruction of main nerve trunks, especially when accompanied by extensive destruction of overlying soft parts, offers unusual difficulties. Also scar tissue contraction and adhesions, even when there is much less damage, may prevent satisfactory results. The methods of dealing with these three conditions here described are neither original nor new. There is a difference of opinion as to their value among neurologic and plastic surgeons who have in the past done most of this reconstruction surgery. The necessity for such reconstructive surgery would be partially eliminated, and its difficulties lessened, if the general surgeon and practitioner who first treats most of these traumatic cases in civil practice could secure clean wounds. Gentleness; the strictest aseptic and antiseptic technic; complete arrest of hemorrhage, even oozing, are the essentials which have been emphasized by Halsted and others, but are still not generally observed. The repair of many simpler injuries is not so difficult but that they could be successfully treated by general surgeons if they would give the subject some study. This was demonstrated in the work of a number of younger, relatively inexperienced surgeons assigned to United States Army Neurosurgical Schools during the World War. The more complicated cases should be referred to neurosurgeons or plastic surgeons early enough to give hope of satisfactory results.

FAT GRAFTS.—Failure to obtain good results in peripheral nerve surgery is frequently caused by scar tissue pressure. This was particularly true of the nerve injuries during the World War: so many wounded lay on battlefields several hours before receiving first-aid treatment that infection was usual, with inevitable formation of extensive scar tissue. The injuries of civil life, many times equalling in destructiveness those of war, are rapidly increasing because of the great number of automobile accidents. Infection of wounds makes immediate nerve operation impossible and the reformation of scar after excision frequently defeats the results of operation. A number of authors have advised placing nerves, freed from scar tissue pressure, in the intramuscular planes, but when a nerve is surrounded by fibrous structures or bone this is impossible. This situation exists when nerves are injured near larger joints: For example, the ulnar nerve at the elbow; the ulnar and median nerves near the wrist where they are surrounded by tendon sheaths and bone; the external popliteal nerve near the knee and the nerve trunks in the neighborhood of the ankle joint. Various materials have been used to protect nerves in such situations: fascial flaps, Cargile membrane, tubulization in preserved veins or arteries, but have been found useless or harmful and have been discarded by practically all surgeons.

Eden and Rehn[1] mention the use of autogenous fat grafts about nerves and tendons as suggested by Henle, at the German Surgical Congress of 1906; also by Lexer, at the German Surgical Congress of 1911. Rehn undertook a study of the question experimentally and in the surgical clinic which formed the basis of a part of Lexer's presentation. They report paralysis resulting from nerve injury and relief by using fat grafts. Neurolysis was necessary to free the nerves from scar tissue in three cases, and a nerve suture was required in one case. The radial nerve (musculospiral) was affected in two instances, the ulnar in a third and the median in a fourth case. These patients were all followed and examined some time after operation; satisfactory recovery was reported in all cases. The length of time under observation varied from 10 to 21 months. The authors believe that the favorable results were dependent upon the use of the fat grafts for protection of the nerves when surrounded by scar tissue. They state that in their previous experience the freeing of nerves from scar tissue alone, without fat grafts, had been unsuccessful. In one case bony callus might have influenced as well as scar tissue, but the result was also satisfactory. In another instance the graft proved successful in spite of wound infection. They believe that there is no other material for transplant which is capable of giving such satisfactory results.

The value of free fat grafts and pedicle flaps was also convincingly presented by Kanavel,[2] in 1916 in a paper prepared for the American Surgical Association. He suggested transplantation of free fat grafts to prevent development of scar tissue about tendons, nerves, and blood vessels, and to restore mobility to joints. Thirty-two patients had been operated upon; five of them for peripheral nerve injuries.

ABBREVIATED REPORTS OF THE FIVE CASES IN DOCTOR KANAVEL'S[2] SERIES WHICH HAD SUSTAINED PERIPHERAL NERVE INJURIES

Case 1.—Division of the ulnar above the elbow with sensory and motor paralysis. The nerve was dissected out of the scar tissue, united, and a pedicle of fat wrapped about it. Examination nearly three years later showed satisfactory restoration of function.

Case 2.—Ulnar paralysis following fracture of right elbow. Nerve dissected from the scar tissue; wrapped in a free fat transplant from the abdomen. Perfect function and sensation were reported two years later.

Case 3.—Median and ulnar nerve divided with entire group of flexor tendons above the wrist. Fat flap from the abdomen was placed along tendons and wrapped about the two nerves. Result reported entirely satisfactory six months later.

Case 4.—Division of median nerve by cut at wrist nine years previously, resulting in loss of sensation over distribution of median; thumb cannot be abducted; nor distal phalanx of thumb flexed; atrophy of the distal phalanges of index and middle fingers. Operation showed stump of flexor longus pollicis united to end of median nerve. Nerve and tendons sutured; free transplant of fat wrapped about nerves and tendons. Result one year later showed perfect function of flexor longus pollicis, some function of abductor of thumb and return of sensation and trophic function to fingers, though still atrophic. Observation not considered long enough to evaluate final result.

Case 5.—Ulnar, median, and musculocutaneous nerves cut above left elbow; wound infected. After the infection had been controlled, the ulnar was transplanted in front of

condyle and ulnar and musculocutaneous sutured and wrapped in fat graft. One year later perfect innervation of ulnar and musculocutaneous, but it was discovered that median had been buried in scar tissue and overlooked. *Second operation gave opportunity to demonstrate loose fatty tissue about the nerves previously sutured.* Median nerve sutured, but not enough time elapsed to show ultimate result.

Kanavel also mentioned the use of a pedicle fat flap sutured into a wound of the forearm, in a patient who had had a serious infection and also a contraction of the hand and an ankylosis of the wrist. A most satisfactory result was apparently obtained. The report of these cases with the results of examination many months or years after operation would seem to afford positive evidence of the value of pedicle fat flaps and free fat transplants. A recent letter states that he still uses them.

Linberg,[3] in 1924, wrote an article on the use of omental fat to prevent scar tissue pressure in nerve operations, and reported the favorable experience of several other Russian surgeons, stating that: Experimentally as well as clinically it had been found, after a long time, that scar tissue did not form in the region of transplanted omental fat.

NERVE TRANSPLANTATION is discussed thoroughly by Stookey.[4] He states that Albert, in 1878, performed the first nerve graft in human surgery, mentioning many other early workers in this field. He credits Huber[5] with the first systematic histologic study of the degeneration and regeneration of a nerve transplant.

A number of surgeons, assigned to the Brain and Nerve Division of the United States Army, during the World War, had the privilege of working with or seeing the results of the work of Dr. G. Carl Huber, Professor of Anatomy at the University of Michigan. Summing up the results of experimental work Doctor Huber[6] states that: "The results of experiments on nerve transplantation indicate clearly that the most favorable results are obtained after autonerve transplant and for practical surgery a cable autonerve transplant using several segments of cutaneous sensory nerve. The type of nerve is not material; funicular arrangement of secondary importance; whether the central or distal end of transplant is placed centrally is not necessary for consideration; accurate end-to-end suture; careful technic; and a dry field are essential." He suggests the cutaneous radial, musculocutaneous and crural nerves as sources for autotransplants. Approximately 70,000 histologic studies by the pyridium silver method showed the results of 21 series of experiments; total 279 operations.

The value of neurotransplants has been variously estimated by the surgeons who were assigned to nerve work during the War, and by others interested in this subject.

Naffziger[7] believes that there are few, if any, satisfactory results from nerve grafting and gives a thorough study of results. He suggests obtaining apposition of divided nerves for direct suture by the following expedients: (1) Free mobilization of the proximal and distal portions of the nerve; (2) transposition to a shorter route than normal; (3) favorable posture

of the extremity to shorten the distance; and (4) gradual lengthening by a two-stage operation.

These measures are also given consideration by Wayne Babcock,[8] but he believes that rerouting should not be employed unless simpler methods fail—damage to the branches of the musculospiral by this method is especially mentioned. He also believes that tissue transplants interfere with the nutrition of damaged nerves and are actually injurious. In summing up his results he states that: "Nerve graft to bridge defects in peripheral nerves should be considered useless and unnecessary."

Thomas and Villandre[9] presented a case of resection of the ulnar nerve for tumor in the forearm (six inches in extent). It was replaced by a transplant from the cutaneous brachii taken from the arm of the patient. Excellent progress in restoration of motor function occurred.

Gosset[10] discussed the permanent results of nerve grafting and reports 35 cases. In 12 of these autografts were used, with five successful results; there was useful motor recovery and sensation; there were also five cases with improvement and two cases of complete failure. Of the five successful cases, two patients were followed for five years, two for six years and one for five months, but this last patient responded to questionnaires, four and also five and one-half years following operation. In four of the five cases, examinations were made by neurologists. He states that results from heterografts were complete failures. The successful grafts were used with moderate-sized nerve trunks of the arm—median, radial, and ulnar nerves. He believes that one would hesitate to graft so large a trunk as the sciatic with such small grafts as can be obtained from the cutaneous brachii and musculocutaneous nerves of the leg, but he has found it much easier to bring the ends together for suture by flexion than with some other nerves. He reviews the work of other French surgeons and reports a success after 26 months following autograft of the radial (musculospiral) nerve obtained by Auvray.

Delageniere[11] reports use of autoplastic graft and expresses the belief that it is possible to obtain complete success with short grafts but doubts the success of grafts longer than 12 cm. (four and four-fifths inches). He had a complete recovery with graft of the radial (musculospiral) nerve; two very fair results with the ulnar nerve, and states that grafts taken from the musculocutaneous nerve of the leg as long as 12 cm. (five and one-fifth inches) have given return of function.

In an extensive discussion of the end-results of peripheral nerve surgery by prominent British surgeons, Sir William Thorburn[12] reported that he had not personally seen successes in the use of nerve grafting, but in the closing discussion stated that some of his "friends in whom he believed, did believe that they had obtained successful results from nerve grafting." Percy Sargent, expressed the belief that nerve grafting "has no particular value." Forrester-Brown reported 643 nerve injuries operated upon in the Edinburgh War Hospital and mentions three nerve grafts with unsatisfactory

results, and also states that the results of neurolysis have not been as good as nerve suture. The statement is made that the grafts were subsequently explored and were found embedded in dense scar. (These last are the type of case in which fat grafts have given satisfactory results in the hands of Kanavel, Rehn, Linberg and other Russian surgeons and which the authors herewith report.) J. L. Joyce reported five cases of free autogenous transplantations without satisfactory results but he does express the belief that autotransplants are "deserving of further study and still have a place in the surgery of injured nerves."

Considering the differences of opinion as to the value of neurotransplants, free fat grafts, and pedicle fat flaps the results in the appended cases are of interest.

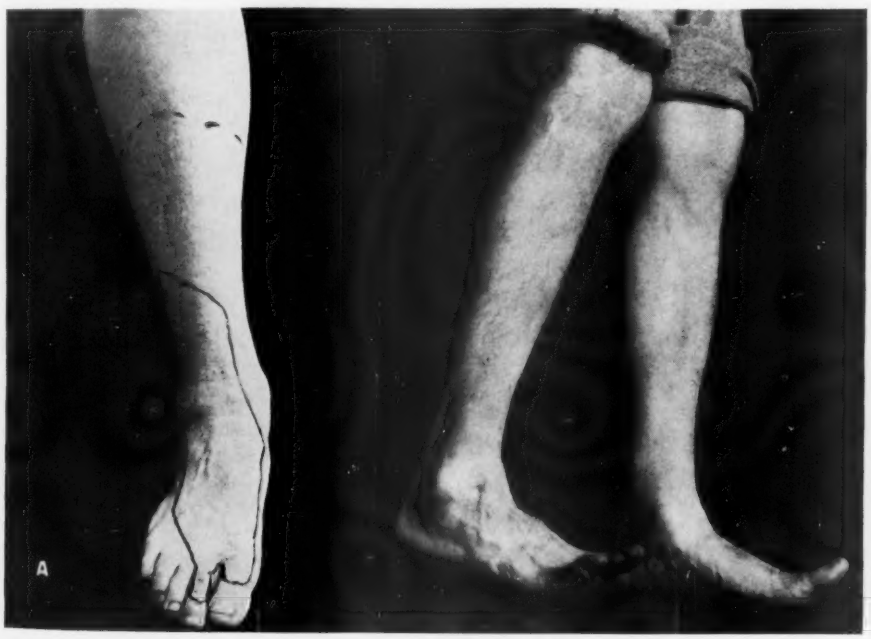

FIG. 1a.—(Case 1.) Showing the area of complete and partial anesthesia immediately following the injury.

FIG. 1b.—(Case 1.) Showing scar of injury and ability to use muscles of injured leg as well as uninjured leg 15 years after operation.

ABBREVIATED REPORTS OF CASES PRESENTED

Case 1.—External popliteal nerve severed just below knee by sharp porcelain fragment from bathtub fixture. Fig. 1a shows the area of complete and partial anesthesia immediately following injury. The severed nerve was surrounded by bone, fibrous tissue and overlying skin; there seemed no possibility of surrounding it by muscle. Dean Lewis[13] states: "The prognosis following external popliteal suture is the worst." He reports only one recovery, and in a relatively high percentage of cases no return of function. Nine months after operation this patient hiked the entire, rough 150 miles of the Long Trail of the Green Mountains and still uses the leg actively in playing tennis, and other sports.

Case 2.—Median nerve injured by penetrating wound by talon of a great horned owl; the patient was assistant in Ornithology at Cornell University. Complete paralysis of sensation and motion in muscles supplied by median nerve below site of injury for 36 days. This injury demonstrates how susceptible nerve trunks are to rough handling and adhesions. Exposure of the nerve did not show division but there were adhesions and abundant evidence of injury. Free fat graft from region of breast placed underneath and over injured nerve gave early return of function. The patient had had quite severe pain and loss of sleep in addition to inability to use his hand following injury. Fig. 2 shows test of function as suggested by Claude (quoted by Pollock[14]).

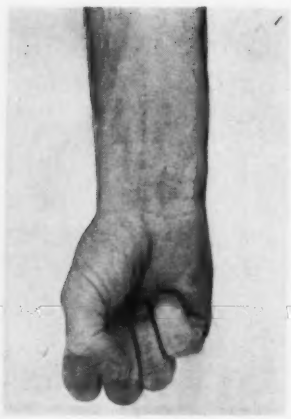

FIG. 2.—(Case 2.) Showing test of function of median nerve as suggested by Claude.

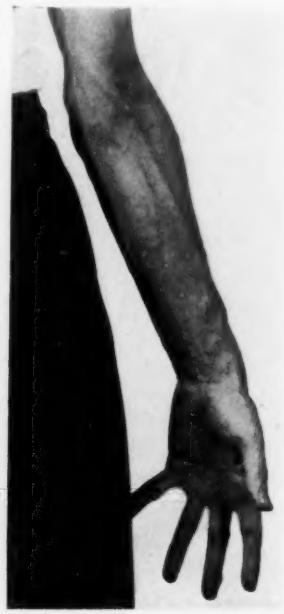

FIG. 3.—(Case 3.) Showing result of neurotransplant in the musculospiral nerve.

Case 3.—An extensive destruction of the radial (musculospiral) nerve of arm from gunshot wound. A cable graft was used which was taken from the external cutaneous nerve of leg. It was possible to place the sutured nerve with the transplant in an intermuscular plane. Examination by Dr. Dean Lewis 18 months after operation showed satisfactory recovery. Fig. 3 shows sign of complete musculospiral motor recovery suggested by Pitres (quoted by Pollock[14]). The fingers are well extended with palm turned to the front. Patient came from Chicago for examination 18 years after operation.

Case 4.—Extensive destruction of soft parts of the forearm together with about three inches of the shaft of the ulna and a long segment of the ulnar nerve. A flap was turned to cover the exposed tendons, thus preventing necrosis. A pedicle flap was used about five months later to supply soft parts sufficient to cover the bone graft for the ulnar defect and transplantation of the ulnar nerve to the front of the forearm and neurotransplant. Bone graft and nerve graft successful 11 years after operation. Patient reports a useful arm 20 years after operation (Fig. 4).

Case 5.—Extensive defect of radius, soft parts and median nerve, the result of a gunshot wound. The soft parts defect was satisfactorily supplied by the transference of a pedicle, full-thickness graft from the chest wall (Fig. 5), which, subsequently, allowed

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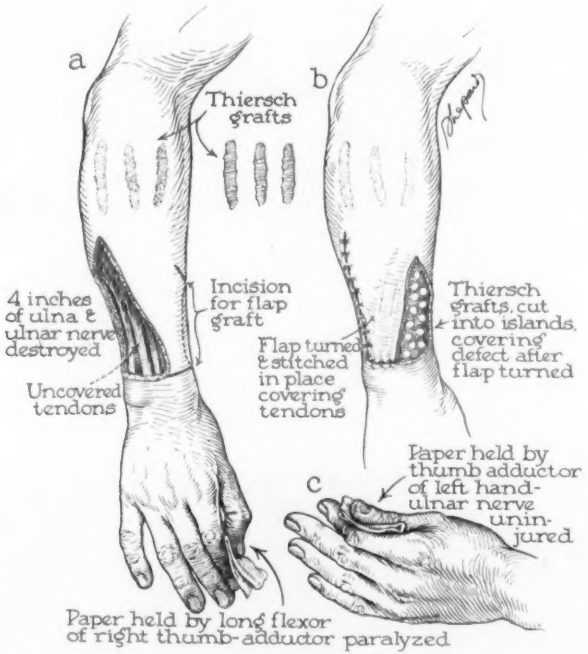

FIG. 4.—(Case 4.) Drawing showing: (a) The extent of the lesion. (b) The result of swinging a pedicle skin and fat flap, and the application of Thiersch grafts. (c) Shows thumb adductor paralyzed and paper held by flexor longus pollicis (innervation median nerve) before repair completed; also paper held by action of adductor pollicis after ulnar nerve function restored.

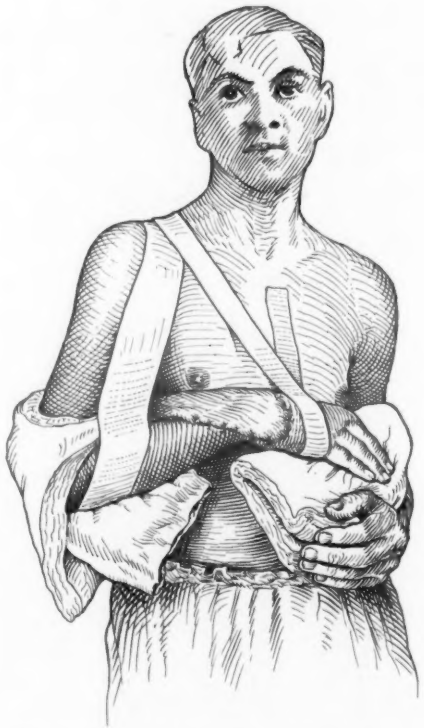

FIG. 5.—(Case 5.) Drawing showing method of application of pedicle graft from chest.

bone and nerve grafts to be effected. The patient has recovered sufficient function to enable him to earn his living.

FAT GRAFTS AND NERVE TRANSPLANTATION

Pedicled flaps have been employed in the practice of one of us for many years and were used at United States General Hospital No. 26 in over 30 cases having extensive destruction of soft parts and underlying structures. They made possible later nerve transplants, bone grafts, freeing of joints, and freeing and suturing tendons or in some instances replacing tendons with fascial grafts. There were no failures of flaps because of unsatisfactory circulation. Long, relatively narrow pedicled flaps, placed parallel to the blood vessels supplying it, have adequate nutrition and the defect is relatively easily closed without undue tension. Rigid fixation with a plaster bandage or other similar material is not necessary, for the success of the flap or comfort of the patient. Small pillows were found comfortable when placed under the elbows of patients with flaps filling defects of the forearms, wrist, or hand. Probably cotton pads would serve the purpose although these small pillows were found more comfortable and more elastic than cotton pads. Adhesive straps were generally used for fixation near the base of the pedicle and a binder pinned tightly and a sling were also used to give fixation and support. There were no complaints of discomfort from the soldiers. Division of the pedicle is usually possible in from 18 to 21 days. It is practically always evident by that time that the circulation is well established. Later operations on nerves, tendons, and bones were delayed for two or three months until one was reasonably certain that the flaps were well established. The chest was usually used, as the blood supply parallels flaps in the direction usually used quite satisfactorily. It is also possible to place the arm in a position which is comfortable.

CONCLUSIONS

The results of a number of competent surgeons of several nationalities, working under varying conditions, would seem to indicate that the methods employed in the cases herewith reported are justified and deserving of further trial in cases of nerve injury.

Neurotransplants have given a sufficient number of good results to warrant their use in cases where extensive destruction of nerves makes any other method unavailable.

Free fat grafts have also given permanent restoration of function in locations where nerves could not be placed in intermuscular planes, and where scar tissue and adhesions had caused permanent disability of fairly long standing.

Pedicle flaps, full thickness skin with fat attached, make it possible to fill large defects caused by destruction of soft parts, permitting reconstructive surgery of nerve, tendon, and bone.

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BRIEF COMMUNICATIONS AND CASE REPORTS

ACUTE TRAUMATIC ABSCESS OF THE BRAIN

CASE REPORT

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THE treatment of cerebral lesions is now, happily, in the hands of specialists who, by prolonged study and wide experience, have developed a technic, both in diagnosis and operative procedure, that has reached a very high grade of efficiency and perfection. The general surgeon rarely assumes the responsibility of entering this special field of surgery but occasionally he is compelled to do so in certain cases of trauma.

The appended case history is reported for several reasons: It illustrates the dangers attendant upon a punctured fracture of the skull; dangers that have been well recognized heretofore and frequently illustrated, particularly during the great war. The case cited occurred 35 years ago at a time when specialism in cerebral lesions was only beginning to be evolved. The patient, age 12, exhibited jacksonian fits due to the development of an acute abscess in the brain. After operation he recovered and now, at the age of 47, he continues to enjoy good health and has never suffered from any recurrence of symptoms referable to his brain injury. It is of interest to note the use of iodoform gauze as an adjunct to the rubber tube in order to secure more adequate drainage. Dr. Joseph E. J. King[1] has recently advocated the use of iodoform gauze in the treatment of acute metastatic brain abscess. He reports a successful case in which gauze alone was used as a drain. He introduces a cone of gauze into the cavity and packs the cavity of the cone with strips of soft, fluffed iodoform gauze. No such elaborate technic was employed by me and yet I regard the use of the gauze pack, although it remained in but a short time (12 hours), as an important factor in securing the subsequent free drainage through the tube.

Case Report.—W. G. O., age 12, was struck on the head, July 12, 1902, by a hay fork weighing about 30 pounds, which had fallen from a considerable height. One of the sharp prongs penetrated his skull, resulting in a punctured fracture of the parietal bone in the rolandic region, laceration of the meninges, with invasion of the brain substance.

The accident occurred on a farm in the country and the doctor who first saw him found a scalp wound one and one-half inches long. One approximating suture was introduced. He told the father he thought the skull was fractured. The patient suffered no untoward symptoms until 4 P.M., July 16, four days after the accident, at which time he suddenly developed an epileptic fit of the jacksonian type. This began with convulsive seizures of the right arm, right leg and right side of the face and then

became general. Fits of similar character were repeated at intervals and became more frequent up to the time he was first seen by me, July 17, five days after the accident. The lad was conscious but was very apprehensive of a recurrent attack.

Operation was immediately undertaken. The head was shaved and scrubbed. Under general anesthesia the scalp wound was enlarged. The hole in the parietal bone was about ½ cm. in diameter with irregular edges. It was situated behind and above the parietal eminence. A button of bone was removed by a trephine, 3.5 cm. in diameter, which included the punctured area. The tip of the finger was inserted, which dislodged something (probably clot) that was obstructing the way. There immediately gushed out, under great pressure, about two or three drachms of blood, blood clot, brain detritis and a little pus. A considerable cavity in the brain was found into which the forefinger could be passed downward and forward for three-fourths of its length. This doubtless indicated the direction taken by the prong of the hay fork. Several spicules of bone were removed from the cavity, which was cleared of its contents. A large drainage tube was secured in position, around which was packed some iodoform gauze. The scalp wound was partly closed by a few sutures of silkworm gut.

After the operation, the patient had several convulsive seizures; one occurring 12 hours postoperative was recorded as "severe." The others were slight. They ceased entirely after two days and did not recur. The tube was removed daily, cleansed and reinserted. It was gradually shortened. The gauze was removed 12 hours after the operation.

The patient made an uninterrupted recovery. He had some weakness of the right leg that persisted for a short time but this disability disappeared entirely. A recent report, nearly 35 years after the operation, shows that he has enjoyed excellent health. He has never had any recurrence of convulsive seizures or any disability referable to his head injury.

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MECKEL'S DIVERTICULUM PERFORATED BY FOREIGN BODY*

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Case Report.—A boy, age 11, was admitted to St. Luke's Hospital, November 27, 1934, complaining of severe pain in the right lower quadrant of his abdomen for the preceding 24 hours. The pain was generalized in the beginning, but during the five or six hours before admission, it showed a tendency to localize in the right lower quadrant. He was nauseated and had vomited twice during this interval. A cathartic and an enema did not effect relief of the pain. The temperature was never higher than 100° F. He had never had such an attack before. The usual childhood diseases were the only illnesses suffered before this attack.

On admission, the temperature was 99.8° F.; pulse, 100; respiration, 22. White blood cells, 15,000; polymorphonuclears, 84 per cent. Examination revealed a picture, typical in every way, of an attack of acute appendicitis, and this was the preoperative diagnosis. He was operated upon immediately, the abdomen being opened through a McBurney incision. The appendix lay in a little pool of lymph but did not look quite bad enough to have caused the acute picture presented. Meckel's diverticulum was the next possibility considered. Eighteen inches from the ileocecal valve, a Meckel's diverticulum four cm.

* Read before the New York Surgical Society, November 11, 1936. Submitted for publication March 1, 1937.

long was found with a foreign body projecting three-quarters of an inch from its tip. The intestine about the diverticulum was red and congested. There was a small amount of serosanguineous fluid present which was cultured. Clamps were placed across the base of the diverticulum which was then excised with actual cautery. The base was sewn over with continuous chromic gut, inverting the cut edges. This was reinforced with a second row of interrupted mattress sutures of the same material. Because of the reaction in the peritonium surrounding the diverticulum, it was thought better to drain, and a small piece of rubber dam was inserted. An appendicectomy was also performed. Convalescence was uneventful; the incision healed by primary union, and the patient was discharged, 13 days postoperative. Culture of the abdominal fluid was sterile.

Pathologic Examination.—Gross: "Meckel's diverticulum four centimeters in length and two centimeters in diameter, slightly constricted near its tip. Penetrating the wall of the tip of the diverticulum and protruding one-half centimeter beyond is a splinter of wood two and one-half centimeters in length. The mucosa is swollen, hyperemic, and covered with thick mucus."

Microscopic Examination.—"The serosa shows little inflammatory change; the lining villi are well preserved, and their epithelial cells contain numerous swollen goblet cells. In areas there is an hyperabundance of mucous secretion and infiltration of stroma and stromal vessels with polymorphonuclear and round cells. There are no areas of gastric mucosa present, and there is no evidence of ulceration.

"The lumen of the appendix is quite wide, its lining epithelium flattened and atrophic. Lymph follicles are prominent with active germinal centers. Some fresh hemorrhages and infiltration with polymorphonuclear cells are present in the mucosal coat. Vessels of muscularis and serosa coats contain numerous polymorphonuclear cells. Diagnosis: Acute appendix."

COMMENT

The lesson to be learned from this case is that it is always a good plan to keep the possibility of Meckel's diverticulum in mind. On several occasions, I have found them present when least suspected. If this appendix had looked a little worse than it did, it would have been easy to be satisfied that it was the cause of the symptoms presented, and thereby to have overlooked the Meckel's diverticulum completely.

Discussion.—Dr. Edward W. Peterson (New York) said that in the Babies' Ward and the general service at the Post-Graduate Hospital, he had encountered a number of instances of Meckel's diverticulum. One case, a 15-year-old girl, gave a history and symptoms quite similar to those of the case presented by Doctor Donovan. Here, too, a diagnosis of acute appendicitis was made, but upon exploration a fish bone perforating a Meckel's diverticulum was found to be the cause of the symptoms. Resection of the diverticulum was followed by prompt recovery. In another instance, which occurred in a six-month-old infant, profuse hemorrhage from an ulcer in a Meckel's diverticulum was the prominent symptom. The pathologic examination of the specimen, removed at operation, showed that the ulcer had developed in aberrant pancreatic tissue present in the diverticulum. A Meckel's diverticulum was also found to be the causative factor in two cases of acute enteric intussusception. The majority of diverticulum cases, however, were discovered incidentally, during the course of operation for other conditions, and gave rise to no symptoms.

MEMOIR

RANDOLPH WINSLOW

1852–1937

Dr. Randolph Winslow, Professor Emeritus of Surgery at the University of Maryland, died in Baltimore February 27, 1937. He was born in North

Randolph Winslow, M.D.

Carolina, October 23, 1852, and was, therefore, in his eighty-fifth year. He

was one of the few survivors of the great era of surgical expansion that began with the achievement of clean surgery and his early record of operative pioneering is proof of this. He was one of the first, if not the first, to introduce antiseptic surgery into Maryland. According to Cordell, Doctor Winslow was the first surgeon in Maryland to resect the pylorus for carcinoma and to shorten the round ligaments (1884). He performed the first vaginal hysterectomy in the State in 1888. He was the first Maryland surgeon to operate successfully for gunshot wound of the intestine (1893).

He was one of the last professors of surgery to come up through the various ranks of assistant demonstrator of anatomy, demonstrator of anatomy and professor of anatomy to the head of the surgical department. There is still something to be said for this system whereby anatomy was taught as an applied science, instead of as a pure one.

At a period when many men entered medical schools with little preliminary education, he brought to the study of medicine a well trained mental equipment, having received both an A.B. and an A.M. degree from Haverford College. He was graduated from the University of Maryland in 1873 at the head of his class. He became Professor of Surgery in 1902, upon the retirement of Dr. Louis McLane Tiffany and continued in this position until his own retirement in 1920.

He earned and deserved distinction in a number of ways aside from the teaching and practice of surgery. His style as a writer was clear and simple and direct and these qualities stood out in his character. He was honest, fearless and forthright, and despised subtlety, subterfuge and sham.

During much of his teaching career, educational standards were low, but he exerted himself constantly to raise the level of scholarship in medical schools and for 20 years was on the Executive Council of the Association of American Medical Colleges. He served the medical profession in many other ways; on the Judicial Council of the American Medical Association, as President of his State Society and at the time of his death was one of its Councillors. He was elected to the American Surgical Association in 1914, to the Southern Surgical Association in 1905, of which he was President in 1921, and was a member of many other local and national groups. He was especially faithful and loyal to the University of Maryland and rendered devoted service to it.

During his long service to his fellows he displayed the changing phases of a useful and successful life; the virile and fighting qualities of a young man, the strength and certainty of the maturer man and, after retirement, he unconsciously gave a fine exhibition of how a strong man grows old; showing qualities of gentleness, kindness, understanding and sympathy with no evidence of bitterness or regret. He continued to take an interest in his profession, his societies, his friends and his school, which made association with him not only an inspiring companionship, but a real joy.

ARTHUR M. SHIPLEY.

BOOK REVIEWS

OPERATIVE SURGERY. By J. Shelton Horsley, M.D., LL.D., and Isaac A. Bigger, M.D. Fourth Edition. Two Volumes. C. V. Mosby Co., St. Louis, 1937.

In 1921, Dr. J. Shelton Horsley published his first work on Operative Surgery. In 1924 and 1928, the second and third editions appeared respectively, each in a single volume. These three editions had been prepared by a general surgeon who was doing his own urologic, orthopedic, plastic and neurologic surgery, and represented, essentially, records of Doctor Horsley's personal experiences. Before undertaking the preparation of the fourth edition of Operative Surgery, Doctor Horsley invited Dr. I. A. Bigger, Professor of Surgery at the Medical College of Virginia, to act as co-author of the work. He realized that the field of general surgery was gradually being narrowed because of the rapid development of the various surgical specialties. Doctor Horsley and Doctor Bigger, therefore, very wisely gathered unto themselves several surgeons, namely: Dr. Donald M. Faulkner, Dr. John S. Horsley, Jr., Dr. C. C. Coleman and Dr. Austin I. Dodson, each one having become established as a specialist in his particular field of work. With a group of authors such as this, the volume of material to be included in Operative Surgery naturally increased so that it was necessary to produce the work in two volumes, which consist of 1,387 pages with 1,259 excellently executed plates and illustrations.

It is interesting to note the development and improvement in these various editions. However, there is one noticeable fact which stands out in all four of them; namely, the emphasis placed upon the importance of physiology and biology to surgery. The authors feel that a beautiful piece of technical surgery, perfectly performed, is poor surgery if the organs so function that the symptoms, of which the patient complained, are not relieved. Doctor Horsley is very insistent that in gastric resection the best results are obtained by flaring the cut end of the duodenum, so that it can be anastomosed directly to the resected end of the stomach. This is only a single example, of which there are innumerable others, of what the author means by physiologic surgery. Dr. J. S. Horsley, Jr., has recorded some interesting experimental work dealing with the ligation of the femoral vein which is followed by as marked improvement in color and warmth of the affected limb as that obtained by anastomosing the vein and artery. He has shown that these anastomoses do not necessarily allow any increased volume of arterial blood to enter the capillary circulation. Experiments reveal that blood returns to the iliac veins through the large collateral veins. In only one case out of 13 dogs, upon which these arterial venous anastomoses had been performed, did the circulation go very far below the knee.

There is a very excellent chapter on the surgery of the blood vessels including the technic of ligation of the various main arteries. About twenty pages are devoted to operations upon fractures. Most of the text, however, concerns itself with a description of the general principles of handling fractures. The operations which are described are those of the more common fractures which one would be apt to meet in a general surgical practice. Operations upon tendons, and joints and descriptions of various amputations occupy the next three chapters. The subject of plastic surgery is very well covered, completely described and excellently illustrated. The various procedures for surgical lesions of the neck, breast, thorax and its viscera conclude the first volume. The surgery of pulmonary tuberculosis is brought up to date.

The second volume deals generally with the surgery of the heart, hernia, abdomen, including the entire gastro-intestinal and genito-urinary tracts and of the central nervous system. Beck's operation for a new blood supply of the heart is described. All of the accepted gastro-intestinal procedures are included. Each one is presented from the standpoint of a practical, clinical surgeon whose results have been proven to be satisfactory, and whose methods have been based upon intensive laboratory study. Mention is made of the surgery of adenomata of the pancreas, also of partial pancreatectomy for hypoglycemia.

There is a brief description of the surgical treatment for essential hypertension, also for bronchial asthma. Because of the limited space devoted to these conditions the authors apparently did not feel that these procedures were sufficiently physiologic, or that they have not proven to be of sufficient surgical value to be recommended. On the other hand, practically every operation that has withstood the acid test of trial and perhaps of error, that has been accepted by the surgical profession, is well described and well illustrated.

The outstanding features of this work on Operative Surgery seem to be: First, the repeated emphasis that is placed upon saving life, relieving pain and restoring function by physiologic and biologic surgery and not by mechanical surgery *per se*. Second, the elimination of superfluous and untried surgical stunts. The authors have renewed our faith in many of the older procedures and at the same time have brought an invigorating message of the newer surgery that has proven to be sound and worthwhile. Third, the text is simple, straightforward, easily read and understood. It is accompanied by profuse, pertinent illustrations, there being nearly one to each printed page.

MERRILL N. FOOTE.

GASTROSCOPY: THE ENDOSCOPIC STUDY OF GASTRIC PATHOLOGY. By Dr. Rudolph Schindler, Associate Clinical Professor of Medicine, University of Chicago, attending gastroscopist Michael Reese Hospital, Chicago, consulting gastroscopist Cook County Hospital, Chicago. 343 pages, with 89 text figures and 96 color reproductions of gastroscopic observations. Preface

by Dr. Walter Lincoln Palmer, Chicago: University of Chicago Press, 1937.

The volume comprises a total of 21 chapters. The one dealing with chronic gastritis is especially valuable and interesting. Of direct interest to surgeons are Chapter XIV, entitled The Postoperative Stomach, and Chapter XVIII, The Relationships between Gastroscopy and Surgery. The author states that the internist who has seen the interior of the stomach through a gastroscope is more appreciative of the importance of this method of diagnosis than is the surgeon. He feels that the combination of roentgenologic and gastroscopic examination should supplant exploratory operation in the diagnosis of gastric carcinoma, or in the determination of its operability, and that surgeons should welcome a method which avoids the surgical risk inseparable from such cases. Throughout the text the author reiterates his belief that "the differential diagnosis between benign and malignant ulcer on the lesser curvature is usually easy by gastroscopy." He also contends that "gastroscopy usually decides this question of the nature" of pyloric obstruction, whether benign or carcinomatous, thus avoiding unnecessary extensive resection when a gastro-enterostomy would suffice. He maintains that the most common reason for failure in gastric surgery is the development of a serious and incurable gastritis, for the recognition of which gastroscopy is indispensable. He is also definitely of the opinion that roentgenologic examination is of no value in the diagnosis of gastritis. He makes only one exception: Namely, the "granulation relief picture" in extremely severe forms of hypertrophic nodular gastritis.

The author lists a wide variety of clinical indications for routine gastroscopy and includes patients with obvious gastric ulcer, gastric carcinoma, and duodenal ulcer. Gross hemorrhage, too often the bête noire of physician and surgeon alike, receives adequate consideration. He points out that very often the roentgenologic examination does not reveal the cause of hemorrhage and that such hemorrhage may have been the result of a severe hemorrhagic gastritis, an hemorrhagic erosion, or a benign tumor; that the massive postoperative hemorrhages are often due to a severe gastritis without gross ulceration. Gastroscopy is indispensable for the detection of such lesions, and sometimes an hemorrhagic ulcer, not demonstrable by the roentgenogram, is also discovered. The procedure can be carried out safely after the hemorrhage has stopped.

This volume has been awaited with keen anticipation by all members of the profession, particularly those interested in this field of medicine. The author needs no introduction. He is generally conceded, both here and abroad, to be the Nestor of gastroscopists. The medical fraternity can consider itself fortunate in having at its disposal such a comprehensive work to which to refer. The present volume promises to be a standard classic for years to come. It is a marked departure from the author's well-known Lehrbuch und Atlas der Gastroscopie, published in 1923. His enthusiasm for this procedure is understandable and pardonable. On the other hand, he frankly informs us that ulcers of the duodenum and pylorus cannot be

seen gastroscopically and that the lesser curvature of the antrum often remains hidden from view. Yet it is at these very sites that the vast majority of gross, chronic, benign and malignant lesions of the upper digestive tract, so readily demonstrated by the experienced roentgenologist, are located. The reviewer is also of the opinion that differential diagnosis between a chronic benign gastric ulcer and a carcinomatous ulcer (not ulcerating carcinoma), especially in the earlier stages of the latter, is impossible gastroscopically in many instances. Nevertheless, regardless of certain inherent shortcomings of the procedure, often surmountable in the individual case, gastroscopy is an indispensable adjunct to gastric diagnosis and therapy.

GEORGE B. EUSTERMAN.

EDITORIAL ADDRESS

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